

July 1980

American Heart Journal

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Contents

Editorial

- Thomas Young M.D. (1773-1829) 1
J. D. Laird Leiden, The Netherlands

Clinical communications

- Heart rate levels and ventricular ectopic activity during cardiac rehabilitation 9
Maarten Simoons M.D., Cees Lap M.D., and Jan Pool M.D., With the technical assistance of Anya Roodenburg and Cecile van Gent, Rotterdam, The Netherlands
- Tocainide therapy for refractory ventricular arrhythmias 15
D. M. Roden M.D., S. B. Peck M.D., S. B. Higgins Ph.D., R. Keith Carr M.Sc., R. F. Smith M.D., J. A. Dales M.D., and R. L. Woolley M.D., Ph.D., Nashville, Tenn.
- The electrophysiologic effects of intravenous lidocaine in the Wolff-Parkinson-White syndrome 23
Peter A. Barrett M.D., F.R.C.P., Michael M. Laks M.D., William J. Mandel M.D., and Isao Yamaguchi M.D., Los Angeles, Calif.
- Rheumatic mitral stenosis: cross-sectional echocardiographic analysis 34
Masahito Naito M.D., Joel Morganroth M.D., T. Joseph Wardell M.D., Chun C. Chen M.D., and Leonard S. Dreyfus M.D., Philadelphia, Pa.

continued on page 7

Vol. 100 No. 1 July 1960 The American Heart Journal is published monthly by The C. V. Mosby Company, 1130 Westline Industrial Drive, St. Louis, Mo. 63111

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Contents continued

Pathology of the heart in acromegaly anatomic findings in 27
autopsied patients 41

J T Lee M.D., F.A.C.C., and Stanley J Grossman Rochester Minn.

Experimental and laboratory reports

Apex and subxiphoid approaches to Ebstein's anomaly using cross-
sectional echocardiography 53

*Tadashi Kambe M.D., Satoshi Ichimiya M.D., Masao Toguchi M.D., Norio Hibi,
M.D., Yoichi Fukui M.D., Kinya Nishimura M.D., Nobuo Sakamoto M.D., and
Yasuo Hoyo M.D. Nagoya Japan*

Repetitive responses to ventricular extrastimuli incidence mechanism
and significance 59

*Ardeshtir Farshidi M.D., Eric L. Michelson M.D., Allan M. Greenspan, M.D., Scott
R. Spielman M.D., Leonard V. Horowitz M.D., and Mark E. Josephson, M.D.,
Philadelphia Pa.*

Cross-sectional echocardiographic study on persistent left superior
vena cava 69

*Norio Hibi M.D., Yoichi Fukui M.D., Kinya Nishimura M.D., Arata Mura M.D.,
Tadashi Kambe M.D., and Nobuo Sakamoto M.D., Nagoya Japan*

Intracardiac phonocardiography in experimental left ventricular
cavity obliteration potential clinical applicability for the distinction
of obliterating left ventricle from hypertrophic obstructive
cardiomyopathy 77

Hani A. Sabbah B.S., Maria Marulli M.D., and Paul D. Stein M.D., Detroit Mich.

Pressure pulse contour analysis in determining the effect of vasodilator
drugs on vascular hemodynamic impedance characteristics in dogs 81

*Larry R. Zobel M.D., Stanley M. Finkelstein Ph.D., Peter F. Carville B.S., and Jav
A. Cohn M.D. Minneapolis Minn.*

Case reports

Left atrial ball thrombus diagnosed by two-dimensional
echocardiography 89

*Kenji Sunagawa M.D., Yasuhiko Orita M.D., Senichi Tanaka M.D., Yutaka Kikuchi,
M.D., Motoomi Nakamura M.D., and Tameo Hirata M.D. Fukuoka Japan*

Unusual manifestations of severe sick sinus syndrome 95

*Bruce M. Marmor M.D., F.A.C.P., and Martin M. Black M.D., F.A.C.C., Syracuse
N.Y.*

Review

Giant cell (cranial) arteritis a clinical review 99

*Kent A. Huston M.D., and Gene G. Hunder M.D., Kansas City Mo. and Rochester
Minn.*

Fundamentals of clinical cardiology

Difficult problems in the diagnosis of chest pain 103

Herbert J. Levine M.D. Boston Mass.

Appraisal and reappraisal of cardiac therapy

The effect of atropine on cardiac arrhythmias and conduction
Part I 119

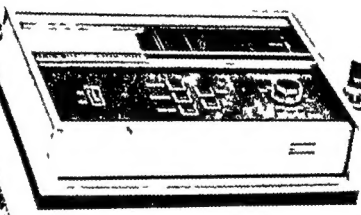
Paul Schweitzer M.D., F.A.C.C., and Herbert Mark M.D., F.A.C.C., Bronx N.Y.

continued on page

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Annotations

Of papillary muscle dysfunction murmurs 128

George E Burch MD New Orleans La

Pacemaker annihilation diagnostic and therapeutic implications 128

J Jaffe MD and C Anteleitch PhD Utica N Y

Common sense and clinical chemistry 130

Flo Lester MB MRCPath London England

Romano Ward syndrome treated by left stellectomy and intracavitary stimulation 131

J M Chaudron MD and F G Lebacqz MD Louvain Belgium

Letters to
the Editor

Central retinal vein thrombosis in a patient with primary pulmonary hypertension 134

S Berliner MD H Dean MD J Shoenfeld MD R Avasar MD and J Pinkhas MD Petah Tikva Israel

Phentolamine and IHSS 134

Eduardo Moreyra MD and Luis E Alday MD FACC Cordoba Argentina

Reply 134

Nicholas Z Aera Dc rou Mich

Prophylaxis of venous thromboembolism 134

R J Farrell and G J Duffy MD Dublin Ireland

Book reviews

Book reviews 136

Books received

Books received 137

Announcements

Announcements 138

(Information for authors on page 17)

(Index to advertisers on page 29)

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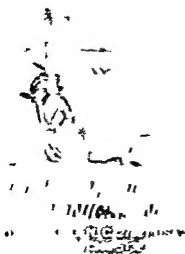
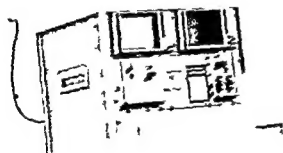
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Contents

- Editorial** The responsibility of the cardiologist mapmaker 139
P G Nixon F.R.C.P. London England
- Clinical communications** Early diagnosis of pericarditis in acute myocardial infarction 144
Jaber I Souaya M.D. Salim A. Mujais M.D. and Haroutune A. Armenian M.D.
Dr P.H. Beirut Lebanon
- Evaluation of the anatomy of congenitally malformed aortic valves by orifice view aortography 152
Gordon M. Folger Jr. M.D. Hans A. Sabbah B.S. and Paul D. Stein M.D. Detroit Mich.
- The clinical importance of cardioselectivity and lipophilicity in beta blockers 160
John M. Crutchshank D.M. M.R.C.P. Macclesfield Cheshire and Manchester England
- Aortic stenosis associated with gastrointestinal bleeding A survey of 612 patients 179
Yehuda Shoenfeld M.D. Michael Eldar M.D. Beni Beda Olsky M.D. Morris J. Levy M.D. and Jack Pankhas M.D. Petah Tikva Israel

continued on page 7

Vol. 100 No. 2, August, 1980 The American Heart Journal is published monthly by The C V Mosby Company 11830 Westline Industrial Drive St. Louis Mo 63141

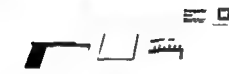
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10/12/1

10/12/1

10/12/1

10/12/1

10/12/1

10/12/1

Management of secondary polycythemia with hypoxic lung disease 267

Ernest L York Richard L Jones Brian J Sproule and Delidas Menon Edmonton
Alberta Canada

Letters to
the Editor

Toxic polyneuritis and toxic hepatitis related to long term perhexiline
maleate therapy 270

Carlo Caruza MD Gianni Caschino MD Walter Troni MD and Rosanna
Cremonesi MD Turin Italy

Reply 271

W A Muir MB MRCP DCH Cardiff Wales United Kingdom

Verapamil therapy 271

Saeed Ahmad MD MRCP FCCP Fairmont W Va

Reply 271

P F Fazio MD F Marchi MD P Pucci MD F Ledda MD and A Mugelli
MD Florence Italy

Book reviews

Book reviews 273

Books received

Books received 273

Announcements

Announcements 274

(Information for authors on page 17)

(Index to advertisers on page 45)

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Contents

| | |
|--------------------------------|--|
| Editorial | Smoking and coronary heart disease: what are we to believe? 275 <i>Carl C Seltzer M.D. Cambridge Mass</i> |
| Clinical communications | Wenckebach second degree A V block in top ranking athletes: an old problem revisited 281 <i>Paolo Zeppilli M.D. Riccardo Fenici M.D. Massimo Sassara M.D. Marco Maria Pirrami M.D. and Cirianni Caselli M.D. Rome Italy</i> |
| | Cross sectional echocardiographic detection of aortic valve prolapse 295 <i>T Joseph Vardella M.D. Joel Morganroth M.D. Masahito Naito M.D. and Chin C Chen M.D. with the technical assistance of Linda Weixell R.D.M.S. and Connie Parrotto Philadelphia Pa</i> |
| | Mitral valve prolapse in anxiety neurosis (panic disorder) 302 <i>Alagirisuami Venkatesh M.D. David L Pauls Ph.D. Raymond Crouse M.D. Russell Noyes Jr M.D. Charles Van Valkenburg M.D. James B Martins M.D. and Richard E Kerber M.D. Iowa City Iowa</i> |
| | Evaluation of left atrial thrombus with computed tomography 308 <i>Haruo Tomoda M.D. Mitsumoto Hoshiai M.D. Ryusuke Tagawa M.D. Shirotsaku Koide M.D. Shaki Kawada M.D. Akira Shatsu M.D. and Seiya Matsuyama M.D. Kanagawa Japan</i> |
| | Acute myocardial infarction in hospitalized patients over age 70 311 <i>Clifton A Lattin M.D. and Mark E Silverman M.D. Atlanta Ga</i> |

continued on page 7

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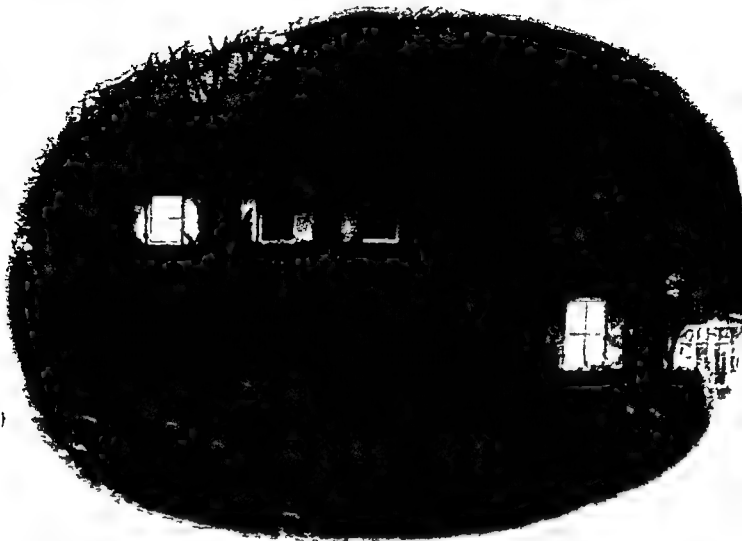
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Contents continued

Experimental and laboratory reports

Effects of angiographic contrast media on colloid oncotic pressure 319
Martin Morissette M.D. Roger M. Gagnon M.D. Jacques Lamoureux M.D. and Jean Lemire M.D. Montreal Quebec Canada

Cardiac lymph and lymphatics in normal and infarcted myocardium 323

Laszlo Szolov M.D. Douglass F. Adams M.D. Norman K. Hollenberg M.D. and Herbert L. Abrams M.D. Boston Mass

Effects of circulatory arrest and rewarming on regional blood flow during surface induced hypothermia 332

Judy Y. Su Ph.D. David W. Amorv Ph.D. M.D. Murray P. Sands and H. Mohr M.D. Dr. Med. Sci. Seattle Wash

Entry of quinidine into cerebrospinal fluid 341

Hermann R. Ochs M.D. David J. Greenblatt M.D. Brian L. Lloyd M.B. B.S. FRACP. Elaine Woo M.D. M. Sonntag M.D. and Thomas W. Smith M.D. Bonn W. Germany and Boston Mass

Case reports

Aprindine psychosis 347

Glenn P. Jacobs M.D. and Ira H. Pores M.D. Newark N.J.

Pseudo tumor of the right ventricular outflow tract and congenital pulmonary valve regurgitation: A case report 349

LCDR J. F. Lut MC USNR CAPT A. D. Hagan MC USN CAPT W. I. R. Veege MC USN CDR S. I. Thompson MC USNR and CAPT B. L. Aaron MC USN San Diego Calif

Review

Myocardial infarct size: Part I: Basic considerations 355

Lionel H. Opie M.D. Cape Town South Africa

Fundamentals of clinical cardiology

Clinical vectorcardiography in adults: Part 2 373

Irvin Hoffman M.D. New Hyde Park and Far Rockaway N.Y.

Appraisal and reappraisal of cardiac therapy

Cardiovascular effects of phenothiazines 397

Uri Elhayim M.D. and William Frishman M.D. Orange Calif. and Bronx N.Y.

Annotations

Limited pressure control to optimum levels may reduce the rate of myocardial infarction in hypertensive subjects 402

I. McD. G. Stewart M.D. FRCP Blackpool England

Exercise and recurrence of myocardial infarction 404

Roy J. Shephard M.D. Ph.D. Toronto Ontario Canada

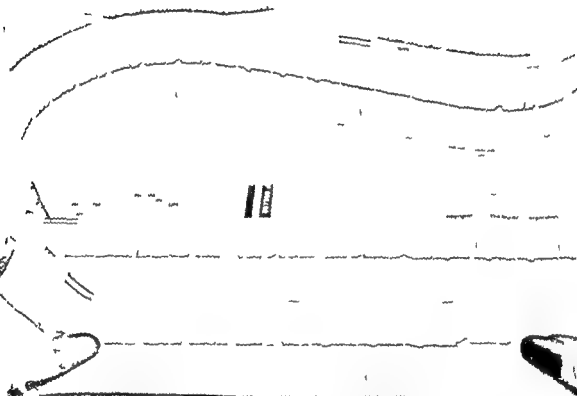
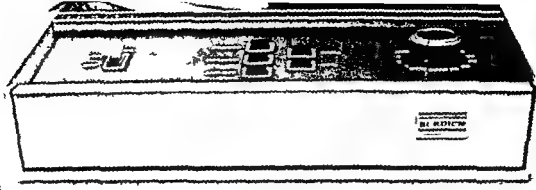
Giant cell arteritis—a cardiological blind spot? 405

Jacques Hou. M.B. MRCP. Ronald W. Strachan M.B. FRCP. and Peter D. Beusher M.D. FRCP. Aberdeen Scotland

Of senile anemia 407

George E. Burch M.D. New Orleans La

continued on page 9



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Contents continued

**Letters to
the Editor**

Effective coronary care and mortality rates 408

A A J Adgey MD FRCA, Belfast Northern Ireland

Reply 408

J R Hampton Nottingham England

Mitral valve prolapse syndrome 409

Dr Zarko Matric kycko Yugo lattia

Spontaneous resumption of sinus rhythm after prolonged AF 409

Abdul Hakim Khan MD Lutwicket h/

Adoption of NIG 409

John H A Brange and Bert B rghust Lucile The Netherlands

Sex and the differential diagnosis of uncomplicated angina pectoris 410

Nicholas W Papaoglou MD Athens Greece

Branham's sign with atrial fibrillation 411

Mayer W Basman MD Jerusalem Israel

Possible association of pneumonitis with amiodarone therapy 412

Heichi H Lotmen ch MD Meir Larin MD Marcel Tupilski MD and Shlomo Laniado MD Tel Aviv Israel

Book reviews

Book reviews 414

Books received

Books received 415

Announcements

Announcements 416

(Information for authors on page 17)

(Index to advertisers on page 56)

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Contents

- Editorials**
- A new approach to improved metabolic control in diabetics: Continuous subcutaneous insulin infusion 417
J C Pickup M.A. B.M. BCh. D Phil London England
- Smoking and coronary disease 421
P R J Burch Ph.D., Leeds England
- Clinical communications**
- Clinicopathological study of the heart and coronary arteries of autopsied cases from the community of Hisayama during a 10-year period: Part IV: QRS waves in the precordial leads 424
Yuichi Hiroshi M.D. Teruo Omasu M.D. Yasuo Hirota M.D. Moriaki Takeshita M.D. Kazuo Ueda M.D. Masahiro Nakano M.D. Seiji Tanaka M.D., Hisao Ikeda M.D. and Shibanosuke Katsuki M.D. Fukuoka Japan
- Hemodynamic correlates of late diastolic posterior motion of the aortic root 433
John A. Ambrose M.D. Eulogio E. Martinez M.D., Jose Meller M.D., Richard Gorlin M.D. Augusto D. Pichard M.D. Michael J. Herman M.D. and Louis E. Teichholz M.D. New York N.Y.
- Angina pectoris and coronary artery disease in patients with severe aortic valvular disease 441
A. Hamid Hakki M.D. Demetrios Lumbiris M.D. Abdulmassih S. Iskandrian M.D., Bernard L. Segal M.D. Gary S. Mintz M.D. and Charles E. Bemis M.D. Philadelphia Pa.

continued on page 7

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Contents continued

Site of origin of ventricular premature beats in patients with mitral valve prolapse 450

Edgar Lichstein MD FAEC Brooklyn NY

Cardiovascular manifestations of tricyclic antidepressant overdose 458

Rene A Langou MD Craig Van Dyke MD Steven R Tahan MD and Lawrence S Cohen MD New Haven Conn

Norepinephrine levels in the coronary sinus in patients with cardiovascular diseases at rest and during isometric handgrip exercise 465

Takashi Haneda MD Yukio Murura MD Tohru Arai MD Toshiyuki Nakajima MD Takiyuki Mura MD Takao Honna MD Kiyoshi Kobayashi MD Hisaichi Sakuma MD Maki Adachi MD Kozumi Mizawa MD Kaoru Yoshinaga MD and Tamotsu Takishima MD Sendai Japan

Cardiac damage caused by direct application of defibrillator shocks to isolated Langendorff perfused rabbit heart 473

Gerrit Koning PhD Adriaan H Veefkind PhD and Hans Schneider PhD Amsterdam The Netherlands

Relation of ventricular premature beat suppression to serum quinidine concentration determined by a new and specific assay 483

Nathan H Carhner MD Michael L Fisher MD William G Crouthamel PhD Prem A Narang MS and Gary D Plotnick MD Baltimore Md

Isovolumic relaxation period in man 490

Basil S Lewis MD MRCP, FCP (SA) Noga Lewis BSc Dan Sapoznikoff MD PhD and Mervyn S Gotsman MD FRCP FACC Jerusalem Israel

The relationship of pulmonary artery wedge pressure to the posterior aortic wall echocardiogram in patients free of obstructive mitral valve disease 500

Alan G Wasserman MD Jerry F Meyer MD FACC and Allan M Ross MD FACC Washington DC

Ischemic cardiomyopathy A clinicopathologic study of fourteen patients 506

Eduard H Schuster MD and Bernadine H Bulkley MD Baltimore Md

Arrhythmias in sleep apnea 513

Tsutomu Imazumi MD Oklahoma City Okla

Echocardiographic features of a stenotic porcine aortic valve 517

Mohsin Alam MD and Sidney Goldstein MD Detroit Mich

Intraventricular thrombosis in polycythemia vera A cause of intractable cardiac failure 520

Majid Ali MD A Olusegun Fayemi MD Daniel Malcolm and Etalynne V Braun MD Teaneck NJ

Echocardiographic diagnosis of left ventricular thrombi 523

Patricia C Come MD John E Markis MD Hugh S Vine MD Barry Sacks MD Colin McArdle MD and Alberto Ramirez MD Boston Mass

Experimental and laboratory reports

Case reports

continued on page 9

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Contents continued

Reviews

Myocardial infarct size Part 2 Comparison of anti infarct effects of beta blockade glucose insulin potassium nitrates and hyaluronidase 531

Leonel H Opie M.D Cape Town South Africa

The pathology of idiopathic hypertrophic subaortic stenosis (hypertrophic cardiomyopathy) A critical review 553

E C J Olsen M.D FRC Path London England

Clinical pathologic conference

Congenital heart disease with trisomy 13 Use of the echocardiogram in delineating the location of a left to right shunt 563

Henry S Cabin M.D Lucille A Lester M.D and William C Roberts M.D., Bethesda Md

Fundamentals of clinical cardiology

The digestive tract as a cause of chest pain 567

William B Long M.D and Sidney Cohen M.D Philadelphia Pa

Appraisal and reappraisal of cardiac therapy

Drug treatment of hyperlipidemia 573

Paul Samuel M.D New York N Y

Annotations

Coxsackieviruses and chronic valvular heart disease 578

A George Chandy T Jacob John and George Cherman Vellore India

Cardiopulmonary resuscitation—an element of sophistication in the 18th century 580

Carl E Bartecchi M.D F.A.C.P., Pueblo Colo

Errors in predicting functional capacity from a treadmill exercise stress test 581

Kerry E Ragg Ph.D Thomas F Murray B.S Linda M Karbonit B.S., and David A Jump B.A Athens Ohio

Of the mitral valve and arrhythmias 583

George E Burch M.D New Orleans La

Alcohol and coronary heart disease 584

Denis A Evans M.D Walter C Willett M.D and Charles H Hennekens M.D Boston Mass

Antithrombotic therapy for saphenous vein bypass grafts? 586

Scott H Goodnight Jr M.D George A Pantley M.D and Shahbudin H Rahumtoola M.B F.R.C.P Portland Ore

Treatment for primary pulmonary hypertension 587

W P Lunke M.D F.R.C.P (C) F.A.C.C Edmonton Alberta Canada

Of walking and dyspnea of congestive heart failure 588

George E Burch M.D New Orleans La

Letters to the Editor

Correlation between exercise hemodynamics and increased magnitude of P terminal force 590

Udupi R Shettigar M.D and Herbert N Hultgren M.D Palo Alto Calif

continued on page 11

Contents continued

Reply 590

Robert DiBianco Washington D C

Function testing soon after acute myocardial infarction 590

John A Vyden M.B. Harvey L. Alpern M.D. Masakuni Kana owa M.D. Elaine Mickle R.N. and Harold B. Rose Sc.D. Los Angeles Calif

Of bibliographies and medical librarians 591

Barbara Bury A.M.L.S. and Daniel Jones M.Ln. San Antonio Texas

Reply 591

George E. Burch M.D. New Orleans La

Migration of redundant pacing electrode 591

M. S. Perelman and M. F. Shui Birmingham England

Reply 592

Gerd Reittig M.D. Homburg/Saar W. Germany

Book reviews

Book reviews 593

Announcements

Announcements 594

(Information for authors on page 19)

(Index to advertisers on page 40)

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Contents

Editorials

Of 1910 595

George E Burch M.D. New Orleans La

Silent subendocardial infarcts fact or fiction? 597

Hubert V Pipberger M.D. and Emigdio A Lopez M.D. Washington DC

Clinical communications

Evaluation of contractile state of the left ventricle from the peak of the first derivative of the apexcardiogram 600

Nikolai S Kolev M.D. Varna Bulgaria

Transesophageal cross sectional echocardiography 605

Kohzoh Hisanaga M.D. Asako Hisanaga B.S. Ka. uhiko Nagata M.D. and Yoshiyasu Ichie M.D. Nagoya Japan

Constituents of the human ventricular myocardium Connective tissue hyperplasia accompanying muscular hypertrophy 610

G William Moore M.D. Ph.D. Grover M Hutchins M.D. Bernadine H Bulkley M.D. Jennifer S Tseng B.A. and Ping F Li B.S. Baltimore Md

Coronary arteriograms and myocardial scintigrams in the electrocardiographic syndrome of septal fibrosis 617

Renzo Romanelli M.D. William H Willis Jr M.D. Winston A Mitchell M.D. and Robert J Boucek M.D. Miami Fla and Loma Linda Calif

continued on page 7

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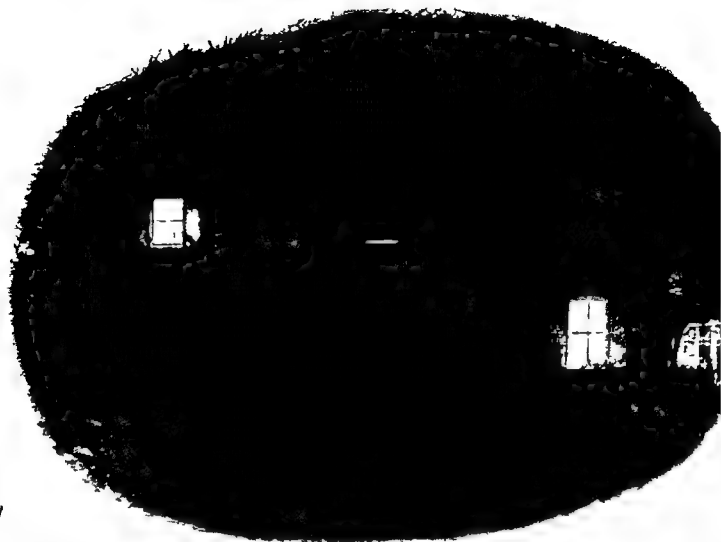
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Contents continued

Long term benefit of dobutamine in patients with congestive cardiomyopathy 622

Donald V. Unverferth M.D. Raymond D. Magorien M.D. Richard P. Lewis M.D. F.A.C.C., and Carl V. Leiser M.D. Columbus Ohio

The long term suppression of ventricular arrhythmia by oral acebutolol in patients with coronary artery disease 631

Neil de Souza M.B. B.S. James J. Kane M.D. Martin L. Murphy M.D. Atul R. Laddu M.D. James E. Doherty M.D. and Joe A. Bissett M.D. Little Rock Ark

Experimental and laboratory reports

Hemodynamic electrocardiographic and metabolic effects of fructose diphosphate on acute myocardial ischemia 639

Angel A. Markos M.D. Nicole C. Oglethorpe M.S., Thomas W. Blake M.D. Patrick H. Lehan M.D. and Harper A. Hellemis M.D. Jackson Miss

Chronic use of aspirin versus indomethacin during non thrombotic myocardial ischemia effects on survival 647

Christos B. Moschos M.D. Bunvad Haider M.D. Amparo J. Escobinas B.S. Ashvinkumar Gandhi M.S. and Timothy J. Regan M.D. Newark N.J.

Site of functional right bundle branch block 653

Chalmers Lyons M.D. F.A.C.C. Salt Lake City Utah and Albany N.Y.

Effect of arterial pressure on left ventricular O₂ consumption coronary blood flow and reserve capacity following coronary occlusion 657

William J. Bugni M.D. Alexandros C. Kralios M.D. Theofilos J. Tsagaris M.D. and Hiroshi Kuda M.D. Salt Lake City Utah

Case reports

Cytomegalovirus myocarditis 667

A. Wink M.D. and H. Schmitz M.D. Freiburg/B. West Germany

Uhl's anomaly with rudimentary pulmonary valve leaflets A clinical hemodynamic angiographic and pathologic study 673

Upendra Kaul M.D. D.M. Ramesh Arora M.D. D.M., and Sudha Rani M.D. New Delhi India

Dissimilar atrial rhythms A patient with triple right atrial rhythm 678

Luis D. Suárez M.D. Andrés Krek. M.D. José A. Alvarez M.D. José A. Martínez Martínez M.D. and Albino V. Perosio M.D. Buenos Aires Argentina

Arrhythmogenic epilepsy an hypothesis 683

Eduard L. C. Pritchett M.D. James O. McNamara M.D. and John J. Gallagher M.D. Durham N.C.

Reviews

Infective endocarditis therapeutic considerations 689

Walter R. Wilson M.D. Donald R. Nichols M.D. Rodney L. Thompson M.D. Emilio R. Giuliano M.D. and Joseph E. Geraci M.D. Rochester Minn.

Neural mechanisms in life threatening arrhythmias 705

Alberto Malliani, M.D. Peter J. Schwartz M.D. and Alberto Zanchetti M.D. Milan Italy

Clinical pathologic conference

Perioperative hypertensive crisis and hemorrhagic diathesis Fatal complication of clinically unsuspected pheochromocytoma 716

J. T. Lie M.D. Byron A. Olney M.D. and John A. Spattell M.D. Rochester Minn.

continued on page 9



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Fundamentals of clinical cardiology

Psychosocial and behavioral influences in the pathogenesis of acquired cardiovascular disease 723

James C Buell MD and Robert S Eliot MD FACC Omaha Nebr

Appraisal and reappraisal of cardiac therapy

Antihypertensive therapy New pharmacological approaches 741

Gordon S Stokes MD FRACP Helen F Oates B.Sc (Hon 1) Ph.D and E Paul MacCarthy MB BCh MRCPJ Sydney Australia

Annotations

When is loss of responsiveness to a vasodilator agent in the patient with congestive heart failure due to tachyphylaxis? 753

Leonard G Meggs MD and Norman K Hollenberg MD Ph.D Boston Mass

Primary myocardial disease diabetes mellitus and small vessel disease 754

Samuel Zonerach MD FACC Gertrude Silverman MD and Olga Zonerach MD FACC Jamaica NY

Exercise rehabilitation of female patients with coronary heart disease 755

N B Oldridge Ph.D D LaSalle M.Sc and V L Jones MD Hamilton Ontario Canada

Of the Q wave and myocardial infarction 757

George E Burch MD New Orleans La

Primary pulmonary hypertension new approaches to therapy 757

Leuis J Rubin MD and Robert H Peter MD Durham NC

Of viral nephritis 759

George E Burch MD New Orleans La

Infectious hazards of mouth to mouth resuscitation 759

Michael R Achon MB FRCP(C) Hamilton Ontario Canada

Risks of anticoagulation during pregnancy 761

Richard M Pauli MD Ph.D Judith G Hall MD and Kathleen M Wilson BA Seattle Wash

Letters to the Editor

Dynamic electrocardiographic recording during sexual activity in recent post myocardial infarction and revascularization patients 763

Vito Paolillo MD Sebastiano Marra MD Felice Spadaccini MD and Pier Federico Angehno MD Turin Italy

Reply 763

Barbara Johnston MD and Gerald F Fletcher MD Atlanta Ga

Pacing below the ventricular rate in terminating ventricular tachycardia and flutter 763

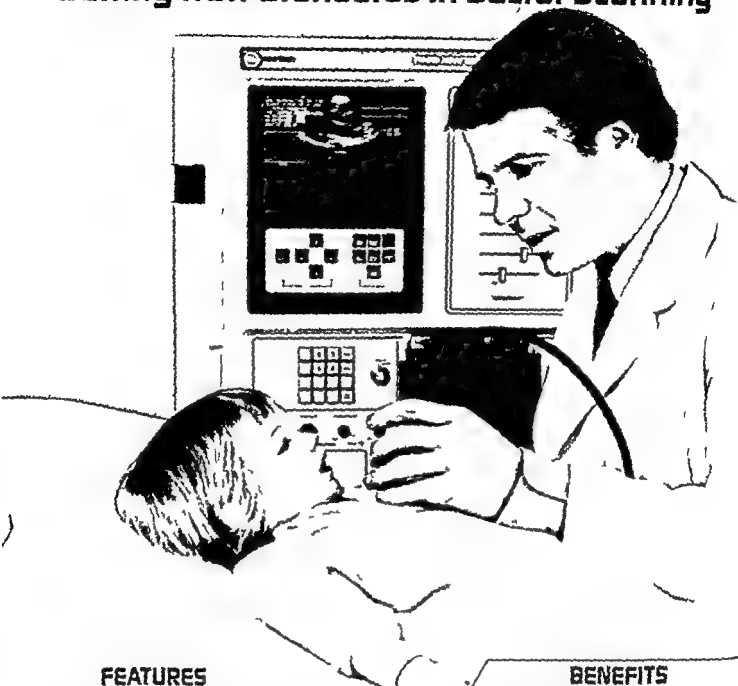
Simion Cotoi Alexandru Incze Constantin Georgescu and Emilian Carasca Tirgu Mures Romania

TTM versus Holter monitoring of symptomatic arrhythmias 764

Una Asst H Weber MD Univ Doz A Steinbach MD Univ Asst G Joskovic M Ph Univ Asst D Glogar MD and Univ Prof K Kaundl MD Vienna Austria

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Contents continued

Reply 765

*Richard S Crodman M.D Robert J Capone M.D and Albert S Most M.D
Providence RI*

Ratios of septum and LV free wall in IHSS and HCM 766

*Jamali G Shakihi MD FACC Fatemeh Reyhani D V M and Iraj Na'anan
MD F.C.A.P. Tehran Iran*

LV hypertrophy versus aneurysm? 767

J E Burns J A C Culham and W J Duncan Toronto Ontario Canada

Reply 768

Amarjit Singh MD Minneapolis Minn

Anomalous ECG and PCG recordings 768

Turkân Gürel MD Ankara Turkey

Reply 768

Lofly L Basta MD FACC FACP MRCP MRCPE Tulsa Okla

Book reviews

Book reviews 769

Books received

Books received 771

Announcements

Announcements 772

(Information for authors on page 19)

(Index to advertisers on page 40)

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Contents

Acknowledgment to reviewers

Acknowledgment to reviewers 773

Special notice

To the readers of the American Heart Journal 775

Editorials

Certain principles in the management of heart disease and pregnancy 775

G E Burch MD New Orleans La

Thermal illness in fun running 778

John R Sutton MB BSc FRCP(C) and Oded Bar Or MD Hamilton Ontario Canada

Clinical communications

Severity of coronary artery disease in patients with diabetes mellitus. Angiographic study of 34 diabetic and 120 nondiabetic patients 782

Carlo Viorito MD Sandro Belocchi MD Giulio Bonanni MD Pietro Giudice MD Domenico Miceli MB Federico Pascone MD and Mario Condorelli MD Naples Italy

Combined mexiletine and amiodarone treatment of refractory recurrent ventricular tachycardia 788

A Waleffe MD PhD L Mary Rabine MD FACC V Legrand MD J Cl Demoulin MD and H F Kulbertus MD FACC Liège Belgium

continued on page 7

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Contents continued

Electrocardiographic left ventricular hypertrophy and coronary artery disease clinical hemodynamic and angiographic correlates 794

Robert I Hamby MD M V Prakash MD Uzair A Wyne MD and Irvin Hoffman MD New Hyde Park Jamaica and Stony Brook N Y

Comparison of the inotropic action of digitalis and isoproterenol in younger and older individuals 802

Dennis V Cokkinos George D Tsatsalis Elias T Heimonas and Constantine D Gardikas Athens Greece

The M mode echocardiogram in Fabry's disease 807

John L Bass MD Savitri Shrivastava MD DM Gregory A Grabowski MD Robert J Desnick MD PhD and James H Moller MD Minneapolis Minn

Silent ST segment deviations and extent of coronary artery disease 813

Steven H Kunkes MD Augusto D Pichard MD FACC Harry Smith Jr PhD Richard Gorlin MD FACC Michael V Herman MD FACC and Joel Kupersmith MD FACC New York N Y

Experimental and laboratory reports

Cross sectional echocardiography III Analysis of mathematic models for quantifying volume of symmetric and asymmetric left ventricles 821

Horace L Wyatt PhD Samuel Meerbaum PhD Ming A Heng MD Pascal Gueret MD and Eliot Corday MD Los Angeles Calif

Recovery time course of ventricular vulnerability after coronary reperfusion in relation to mitochondrial function in ischemic myocardium 829

Satoru Sugiyama MD Takayuki Otsu MD Tadaaki Kato MD and Shohachi Suzuki MD Nagoya Japan

An electrocardiographic-pathologic correlative study on left axis deviation in hypertensive hearts 838

Tatsuji Takagi MD and Ryozo Okada MD Tokyo Japan

Transfemoral temporary pacing and deep vein thrombosis 847

Natesa G Pandian MD Bernard D Kosowsky MD and Victor Gurewich MD Boston Mass

The effects of vasoconstriction on experimental coronary artery stenosis 852

William P Santamore PhD Paul Walinsky MD Alfred A Bove MD PhD FACC Robert H Cox PhD Rita A Carey PhD and James F Spann MD FACC Philadelphia Pa

Case reports

Right ventricular endomyocardial fibrosis simulating Ebstein's anomaly 859

Massoud Alipour MD FRCP (C) FACC Cyavoush Tarbiat MD and Iraj Nazarian MD Tehran Iran

Congenital pericardial defect associated with cardiac incarceration Case report 866

Reiko Saito and Futosumi Hotta Tokyo Japan

Right ventricular myxoma Case report and review of phonocardiographic and auscultatory manifestations 871

Yoshiyuki Hada MD Carla Wolfe Gordon F Murray MD and Ernest Craige MD Chapel Hill N C

continued on page 9



Contents continued

Torques de pointes as a manifestation of mexiletine toxicity 878
C Cocco MD C Stroz MD D Chu PhD and R Pansini MD Ferrara Italy

Reviews

Cardioversion and defibrillation 881
Regis A DeSilva MB FRCP(C) Thomas B Graboyes MD Philip J Podrid MD and Bernard Loun MD Boston Mass

Rickettsial vasculitis 896
David H Walker MD and William D Mattern MD Chapel Hill N C

Clinical pathologic conference

Delayed acute myocardial infarction after blunt chest trauma in a young woman 907
Stephen C May MD David S Blumenthal MD Dolores Shoback MD Sam Fehr MD and Bernadine H Bulkley MD Baltimore Md

Fundamentals of clinical cardiology

On the elastic and rigid forms of constrictive pericarditis 917
E William Hancock MD Stanford Calif

Appraisal and reappraisal of cardiac therapy

Diet in the treatment of hyperlipidemia 924
Morton Sprit MD New York N Y

Annotations

The importance of the history in the medical clinic and the cost of unnecessary tests 928
Gerald Sandler MD Barnsley England

Of saphenous vein arteriosclerosis 931
George E Burch MD New Orleans La

Asymmetric septal hypertrophy in conditions other than IHSS 931
D R Ramsdale BSc MBCHB MRCP and D H Bennett MD MRCP, Manchester England

Autoaddiction a hypothesis on hunger and obesity 933
R F McCloy FRCS and James McCloy DFC BSc Northampton England

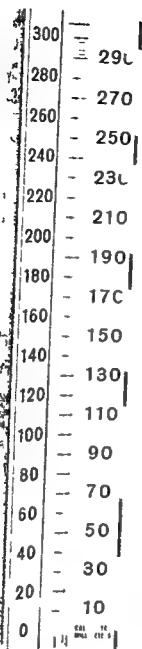
Effect of oral disopyramide on serum digoxin levels A prospective study 934
Hein J J Wellens MD Anton P Gorgels MD Simon J Braat MD Frans W Bor MD Edgar J Vanagt MD and Bob Phaf PhD Maastricht The Netherlands

The role of angiotensin II in the development of peripheral vasoconstriction during open heart surgery 935
K M Taylor MD FRCS W H Bain MD FRCS and J J Morton PhD Glasgow Scotland

Extracranial to intracranial microvascularization for the treatment of completed ischemic stroke 937
R M Greenhalgh MA MChir FRCS R D Illingworth FRCS J McFie MA MD SP Mills BA G R Perkin MRCP and F Clifford Rose FRCP London England

Of cardiac causalgia Horner's syndrome and the cardiac dermatome 938
George E Burch MD New Orleans La

continued on page 11



Continued
on next page

Contents continued

Letters to the Editor

Mitral prosthetic dehiscence and paraprosthetic regurgitation 940

Markku J Ikaheimo MD Oulu Finland

Reply 940

Patrick A C Chun MD Sol I Raffter MD Dennis J Donohue MD Thomas E Bouen MD and James E Davis MD Washington D C

Idiopathic mitral valve prolapse and sudden death 941

Rav C Anderson MD PhD Minneapolis Minn

Reply 942

Aubrey Leatham and Wallace Bridgen London England

On rheumatic fever in children 942

Iraj Arjanzpur Kashani MD FACC La Jolla Calif

Reply 943

Germano DiSciascio MD and Angelo Taranta MD Birmingham Ala and Valhalla N Y

Beta blockers and running 943

Lennart Kayser Peter Kayser Jan Karlsson and Stephan Rosner Stockholm Sweden

Reply 944

Adrian J William MB MRCP (Lond) Los Angeles Calif

Lo—the poor Eskimo? 944

O Schaefer MD FRCP(C) Edmonton Alberta Canada

Reply 945

Kurt A Oster MD Bridgeport Conn

Rupture of myocardium and mitral valve replacement 946

W Alison Ross MA and Daniel D Streeter Jr PhD Seattle Wash

Reply 946

W Woodfin Cobbs Jr MD Atlanta Ga

Cyclophosphamide cardiomyopathy 946

Raymond W Roberts PharmD Jacksonville Fla

Reply 947

I Craig Henderson MD and E Frei III MD Boston Mass

Effects of antiarrhythmics in ischemic models 947

Jerry L Bauman PharmD Robert A Curtis PharmD and Joel O Cousinsky Chicago Ill and Kansas City Mo

Serum myoglobin as a sensitive index of myocardial infarction 948

E Grenadier S Keidar and A Palant Haifa Israel

Reply 949

Carl L Tommaso MD Chicago Ill

continued on page 13


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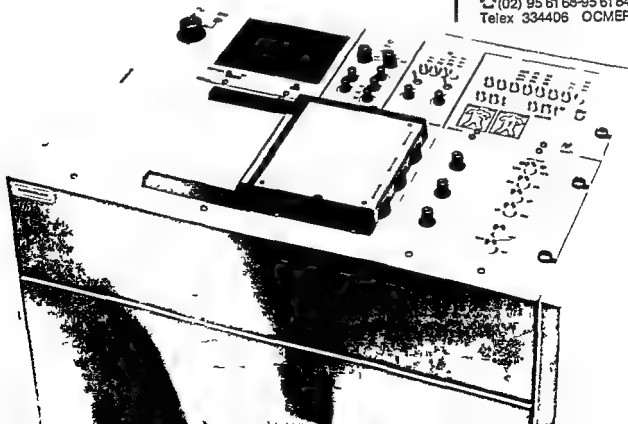
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Contents continued

ook reviews

Book reviews 951

ooks received

Books received 951

nnouncements

Announcements 952

ndex

Author index 955

Subject index 963

(Information for authors on page 19)

(Index to advertisers on page 32)

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December 1980 Volume 100 Number 6 part 2

PROCEEDINGS OF THE

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Contents

Introduction

Introduction 977

Donald C Harrison MD

I Comparative evaluation of new antiarrhythmic agents

Comparative pharmacokinetics of new antiarrhythmic drugs 978

Robert A Ronfeld PhD Framingham Mass

Hemodynamic effects of newer antiarrhythmic drugs 984

David E Jewitt MB London England

Comparison of newer antiarrhythmic agents 990

T D V Laurie MD Glasgow Scotland

II Evaluation of antiarrhythmic drugs in acute myocardial infarction

Placebo controlled study of prophylaxis of ventricular arrhythmias in acute myocardial infarction 995

Ronald W F Campbell MD Newcastle upon Tyne England

Hemodynamic and antiarrhythmic effects of tocainide in patients with acute myocardial infarction 1000

Oluf Nyquist MD Cunilla Forsell MD Rolf Nordlander MD and Karin Schenck Gustafsson MD Stockholm Sweden

continued on page 4

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Prophylaxis of ventricular tachyarrhythmias with intravenous and oral tocainide in patients with and recovering from acute myocardial infarction 1006

Lars Ryden M.D. Krister Arnman M.D. Thor Bjorn Conradson M.D. Stefan Hofvendahl M.D. Ole Mortensen M.D. and Peter Smedgard M.D. Skovde and Helsingborg Sweden

Tocainide for refractory ventricular arrhythmias of myocardial infarction 1013

Charles I Hoffajee M.B. Joseph S Alpert M.D. and James E Dalen M.D. Worcester Mass

Chronic tocainide therapy studies

A prospective randomized trial of tocainide in patients following myocardial infarction 1017

B C Bastian M.B. Ch.B. P W Macfarlane B.Sc. Ph.D. J H McLauchlan M.B. Ch.B. D Ballantyne M.D. R Clark M.B., Ch.B. M S Hillis M.B. Ch.B., A P Rae B.Sc. M.B. and I Hutton M.D., Glasgow Scotland

Open clinical studies at a referral center Chronic maintenance tocainide therapy in patients with recurrent sustained ventricular tachycardia refractory to conventional antiarrhythmic agents 1023

James D Malonev M.D., Roger G Nussen M.D. and J M McColgan B.S. Rochester Minn

Tocainide for drug resistant ventricular arrhythmias Efficacy side effects and lidocaine responsiveness for predicting tocainide success 1031

Roger A Winkle M.D., Jay W Mason M.D. and Donald C Harrison M.D. Stanford Calif

Safety evaluation of tocainide in the American Emergency Use Program 1037

Howard R Horn M.D. Zareh Hadadian Ph.D. Jeanne L Johnson A.B., Helen G Vassallo Ph.D., John H Williams M.D. and Michael D Young M.D. Ph.D., Framingham Mass

Treatment of ventricular arrhythmias with oral tocainide 1041

Michael D Young M.D., Ph.D. Zareh Hadadian Ph.D. Howard R Horn M.D. Jeanne L. Johnson A.B., and Helen G Vassallo Ph.D. Framingham Mass

Antiarrhythmic studies with newer agents

Encainide A new and potent antiarrhythmic agent 1046

Donald C Harrison M.D., Roger Winkle M.D., Magdi Sami M.D. and Jay Mason M.D., Stanford Calif., and Montreal Canada

Studies with aprindine 1055

Douglas P Zipes M.D., Victor Elharrar Ph.D. Robert F Gilmour Jr Ph.D. James J Heger M.D., and Eric N Prystowsky M.D. Indianapolis Ind

Amiodarone in the treatment of cardiac arrhythmias in children One hundred thirty five cases 1063

Philippe Coumel M.D., and Jean Fidelle M.D. Paris and Les Loges-en-Josas France

The clinical use of intravenous verapamil 1070

Les Samroth, M.D., Johannesburg South Africa

Contents continued

V Other antiarrhythmic studies

Hemodynamic and electrophysiologic interactions between antiarrhythmic drugs and beta blockers with special reference to tocainide 1076

Hamid Ikram M.D. Christchurch New Zealand

Shortcomings of the Lown grading system for observational or experimental studies in ischemic heart disease 1081

J. Thomas Bigger Jr. M.D. and Francis M. Weld M.D. New York N.Y.

The automatic implantable defibrillator 1089

M. Mironski M.D. Morton M. Mower M.D. and Philip R. Reid M.D. Baltimore Md.

Clinical use of an implantable automatic tachycardia terminating pacemaker 1093

Jerry C. Griffin M.D. Jay W. Mason M.D. and Richard V. Calfee Ph.D. Stanford Calif. and Freeport Tex.

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American Heart Journal

July 1980 Volume 100 Number 1

Editorial

Thomas Young, M.D. (1773-1829)

The mechanical motions which take place in an animal body are regulated by the same general laws as the motions of unanimate bodies
Thomas Young 1808

J. D. Laird

Leiden, The Netherlands

Thomas Young, physician, natural philosopher and philologist, possessed beyond doubt one of the truly greatest minds at work in the eighteenth century. He drew to a close. His contributions to our understanding of both ourselves and the world around us were legion and although this by itself would be reason enough for a few moments' reflection and indeed homage in 1980 I feel compelled to seek further rationalization for intruding on the busy schedule of the cardiovascular specialist.

A Frenchman¹ said to have remarked when considering the contribution of William Harvey that the facts were all there and indeed were so simple that any schoolboy would have been able to put them together. It was nonetheless Harvey who did so. And where is that clever schoolboy at this point of time in the evolution of our understanding of cardiovascular disease and particularly of ischemic heart disease? This multifactorial disease seems to present an intellectual challenge just beyond the grasp of the established investigators of today. Was it really so much easier in the good old days when the body of knowledge was so much smaller that one person

could develop a commanding knowledge over a broad area of science? I doubt it.

We are not the first generation forced to grapple with concepts beyond both our reach and understanding so perhaps we can profit from considering the accomplishments and indeed the failures of one of the most adroit interdisciplinary intellects of all time. Books have been written (see bibliography) about Thomas Young's many and varied accomplishments and in the short space of this article I wish to call attention to some of his lesser contributions of particular interest to the cardiovascular specialist. For it is the curious burden to be borne by the greats that these lesser contributions often fail to receive the attention they deserve. Achievements which for a lesser mortal might constitute success beyond imagination are doomed to be forgotten so overshadowed are they by other pinnacles of intellectual brilliance. And so it was with the lesser contributions of Thomas Young. As great as they were, they paled when seen in the light of his brilliant discovery of the principle of wave interference of light, his unravelling of some of the mysteries of physiological optics, or his discovery of the clue to the decipherment of the Rosetta Stone, eventually leading the western world to the key for unlocking the cultural treasures of ancient Egypt.

Was it his genetic material or the environment of his youth which fell a goodly number of standard deviations away from the mean of his

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Fig 1 Thomas Young MD FRS from an engraving by Henry Adlard based on the portrait by Sir Thomas Lawrence (1781) showing Dr Young at age 44 (Photo with the kind permission of the Science Museum London)

fellow men? Probably both but in what measure each contributed to his genius is unknown and every proposition is pure conjecture.

The 11th of June 1773 does not catch England at its best. As personal intolerance was on the increase at home turbulence and conflagration became more and more characteristic of foreign affairs. In the western counties of England little of this could be felt and such was the isolation that the little village of Milverton eight miles from Exeter in the county of Somerset knew little more of the world than the decline of the wool industry for such the backbone of the local agricultural economy. Young's father Thomas Young was a very successful and diversified mercer and banker. As for the rural life of Milverton so enervated was it that the intellectual and cultural life of Thomas Young was far more important than the conventional stability of his contemporaries were their nations. They

were members of the Society of Friends or Quakers. Although tolerance was on the rise again this was not an easy thing to be in the England of 1773. The scars both literal and cultural on the family circle plus the dogma of this faith itself fostered an intense adherence to the serious strictures of the sect as well as stimulating a nearly obsessive self reliance and personal responsibility. The Quakers belief in an inner light and the obligation of each individual to continually search in and through himself for the truth formed a driving force in Thomas Young's early education which is difficult to imagine today.

A compilation of his early education is enough to cause the present day student of medicine or physics including this author to stop be silent and reflect for a few moments. Upon reaching the age of two he had learned to read with in his own words considerable fluency and before reaching the grand age of four had read the bible twice through. For unclear reasons he spent the better part of his first seven years with his maternal grandfather Robert Davis in Minehead. One reason may simply have been practical he was the eldest of ten children or it may have been the early recognition that this genius required special care. In any event he soon became a favorite of Mr Davis. Young Thomas apparently took to heart the oft repeated admonishment of his grandfather that 'A little learning is a dangerous thing. Drink deep or taste not the Pierian spring. After an abortive year and a half at a miserable boarding school he spent six months of his eighth year at home. In these months he spent a good deal of time at the home of his neighbour a Mr Kingdon a practical man of great ingenuity who had raised himself from tailor to land surveyor. This encounter is significant for its demonstration of an early interest in science. There he found many books relating to science and particularly a Dictionary of Arts and Sciences in three volumes folio which he began to read with the most intense interest and delight. At this house he also found several mathematical and philosophical instruments. The following spring when nearly nine years old he was sent off to a boarding school in Compton Dorset. The Compton school's contribution to the nurturing of the phenomenon Young appears to consist of equal parts classical education with emphasis on Greek Latin French Italian and Hebrew and the informal education provided by Mr Josiah

Jeffrey the school s usher and apparently also its entrepreneur It seems he had a lively private trade going with the young scholars in paper copper plates copy books and colours Jeffrey lent Young *Martin s Lectures on Natural Philosophy* the optical part of which especially caught the boy s fancy The pre teen Young under the tutelage of Jeffrey further broadened his skills by learning the use of a lathe the making of a telescope grinding and preparation of colours and the binding of books Already he apparently demonstrated a nearly obsessive and jealous guarding of his precious time which as his biographer Wood demonstrates he quite literally carried to his deathbed In his own words I was in the habit of rising an hour sooner than my school fellows in summer and of going to bed an hour or two later in winter for the purpose of mastering my lesson for the day my school business was thus soon finished

None of the writings concerning Thomas Young give any really clear indication of the process by which his career choice was made Apparently it was just as random a process as with more mortal souls As fate would have it his uncle was the very successful rich and influential physician Richard Brockelsby (1722 1797) Before leaving school at the age of 13 Thomas had a brief encounter with Morris Birkbeck from which he imbibed a wish to study Botany This wish apparently took a turn later towards Medicine though not before he acquired a lathe of his own and had made himself a microscope Via a complex net of family and Quaker friends arrangements were made for his further education At 14 he was sent off to Youngsbury to become the study companion of Hudson Gurney (1777 1864) who later became a rather well known antiquary writer and member of parliament Both boys labored under their tutor a well respected and some say brilliant John Hodgkin However there seems to be in the case of Young some uncertainty with respect to who was doing the tutoring Method notwithstanding Young s knowledge of languages flourished in this period and a copybook containing extracts of the Bible in English French Italian Greek Hebrew Chaldee Syriac Samaritan Arabic Persian Turkish and Aethiopic are admired by his biographer Peacock for of all things their beautiful penmanship

This period of intense scholarship and accom-

plishment was suddenly interrupted at the age of 16 by a serious respiratory illness verging on consumption With careful nursing he eventually recovered though it was apparently serious enough to elicit a letter from his physician uncle Richard Brockelsby admonishing him to take better care of himself and expressing the opinion that eating a little fish twice or thrice a week would do no harm but you must make the trial cautiously In the same letter his uncle takes Thomas to task for his prudery about abstaining from the use of sugar on account of the Negro Trade In those times this was a form of symbolic protest fairly common among Quakers and other activists

By the time he left Youngsbury at the age of 19 not only was his classical education up to a level which allowed him to discuss as an equal with the scholars of his time but moreover he was widely read in science having ploughed through the works of Newton Linnaeus Lavoisier and Black and Boerhaave

He spent little time at home during this period and four months each winter were spent in the London home of the Barclays in Red Lion Square This seemingly insignificant fact is nonetheless noteworthy for it gives us a hint of the process by which Young s eventual career choice was made It was a chance for Young to sample the civilized life of cultured London to attend concerts lectures to move in literary circles to polish his social graces and to try out his intellect against worthy competition Moreover it was in the periods of his London residence that his remarkable abilities came to the attention of his uncle Brockelsby who it would appear was largely responsible for steering Thomas Young in the direction of Medicine

As an interesting aside the practice of medicine was in those days still referred to as the practice of Physic whereas what we now call physics was termed Natural Philosophy the quite arbitrary and artificial distinction between the two fields being hidden by changes of language Both Physics and Physician stem from the Greek φυσικος meaning Natural

Young s approach to problems was strongly influenced by firm belief in several guiding principles As I have already mentioned he jealously guarded his life against the dangers of wasting time Hudson Gurney his study companion wrote of Young that at no period of his life

was he particularly fond of repeating experiments or even of very frequently attempting to originate new ones considering that however necessary to the advancement of science they demanded a great sacrifice of time, and that when the fact was once established that time was better employed in considering the purposes to which it might be applied or the principles which it might tend to elucidate. Moreover he was personally persuaded of both the effectiveness and advantage of self study and at 19 wrote to his brother, Robert

Although I have readily fallen in with the idea of assisting you in your learning yet it is in reality very little that a person who is seriously and industriously disposed to improve may not obtain from books with more advantage than from a living instructor. Something is wanting for the direction of application in the right path but it must be the strength of the traveller and not of the guide that must conquer the difficulties of the journey. Masters and mistresses are very necessary to compensate for want of inclination and exertion but whoever would arrive at excellence must be self taught.

As Peacock asks: What then were the primary causes of the extraordinary success of an education conducted for so many years with so little communication with other minds with so little assistance from extrinsic sources? The principal of these must be referred to the peculiar constitution of his own mind to his great industry, to the conviction which he always felt that what one man had accomplished another might accomplish also.

Young himself in a letter to his uncle in 1792 quotes some lines of a poem by Barnard as expressing his view. Thou sayest not only skill is gained. But genius too may be obtained by studious imitation. Peacock continues: He had little faith in any peculiar gifts of genius believing the original difference between human intellects to be much less considerable than it was generally supposed to be. His temper also in early youth was singularly unruffled and tranquil he had no boyish tastes or amusements he was educated by no dreams of the imagination from the assiduous cultivation of understanding. This briefly was the young man of 19 who set off to London to study medicine in 1792.

Young followed lectures in the Hunterian School of Anatomy founded by William Hunter and set forth by Baillie and Cruikshank. It is

difficult to visualize today but in those days the 'West End' was still very nearly just that and the anatomy lectures were held in a small building on Great Windmill Street which has long since been incorporated into the Lyric Theatre on Shaftsbury Avenue. It would appear that the interest in Anatomy in the Soho district of London has deeper cultural roots than might at first be evident.

Young was very quick to distinguish himself demonstrating his almost uncanny ability to reach into his already vast store of knowledge (in this case, optics) and apply it to his current area of study. While dissecting the eye of a recently slaughtered ox he became intrigued by the mechanism of accommodation. His investigations led him to the conclusion among other things that variation of the focal length of the lens itself was responsible. Young communicated his finding in a paper read to the Royal Society in May 1793. This paper by a second year student caused something of a stir embroiling him in a not altogether pleasant debate concerning both the correctness and the originality of his work. While others debated the latter Young himself questioned the former. Both were eventually resolved and in the summer of 1794 Young was elected to Fellowship of the Royal Society on the strength of this work.

Having begun with something of a splash Young on whose advice is not clear journeyed on horseback to Edinburgh to continue his studies. Armed with letters of introduction and a curiosity as broad as his knowledge he made quite a tour of it. In his travels through Derbyshire and Yorkshire he examined with his accustomed activity and intelligence the collections of art or natural history mines mineral springs manufactures or other curiosities. Having spent some time visiting Erasmus Darwin the grandfather of the great naturalist he left with yet another letter of introduction to an Edinburgh friend stating: He unites the scholar with the philosopher and the cultivation of modern arts with the simplicity of ancient manners.

The medical school of Edinburgh then so highly regarded by most did not escape without the criticism of its new student. While he later concludes that Edinburgh had much to recommend it to the student of medicine he was able to share his attention between his study and taking flute lessons learning to dance to enjoy the

theater and other naughty things he had missed in his strict upbringing. I hasten to add that the list of activities makes very light reading by current standards.

Having taught himself German, he set off to continue his studies in Göttingen, and so it was that on the 10th October he left Yarmouth on the packet boat. Although the university enjoyed a very high reputation at that time, Young was not sad to leave with his doctorate. In July 1796, he had already become accustomed to being treated as an equal by the respected top, and found the formality of German university life not his cup of tea.

It would seem that professional bureaucracy is not a new invention. For on his return to England, Young, ready to practice medicine, was tripped up by the fine print of regulations. Although a bit oversimplified, the practical consequence of the rules was that in order to become a fellow of the College of Physicians, a degree from either Oxford or Cambridge was required. Thus, rather reluctantly and largely as an expedient, he entered Emanuel College, Cambridge, and shall barely keep the term for two years, which will be more convenient to me than

His lack of commitment to his formal study in Cambridge did give him the spare time for an active social life as well as the opportunity to do some experimental work on the propagation and character of both sound and light waves. These ideas first occurred to Young while he was working on his dissertation in Göttingen, and were written up in the summer of 1799, after his completion of the required six terms of residence in Cambridge. Thus, in the last year of the 18th century, Thomas Young set off on his dual career as physicist and physician.

It is hard to believe that just one man was responsible for his output during that first decade of the 19th century.

In 1801, he was appointed Professor of Natural Philosophy at the recently founded Royal Institution, and began at once preparing a Course of Lectures on Natural Philosophy and the Mechanical Arts. Young set as his goal a complete review of the state of knowledge in Physics up to that point, and attempted to cast it all in language suitable for a mixed audience.

The enormous diversity of his mind is nowhere more evident than in these lectures. It is easy to presume that in those days the body of knowledge

was so circumscribed that all that was known could be comprehended by one albeit clever man. Those were the days when a physician could do fundamental and significant research in physics—the days before the information explosion before the Xerox machine. It was therefore something of a shock to note Thomas Young's words in the Preface to the published lecture notes which appeared in 1807: "I had in some measure pledged myself to make a catalogue of the best works already published on the several subjects, with reference to such passages as appeared to be most important." Hence arose a catalogue of references, respecting which it is sufficient to say that the labour of arranging about twenty thousand articles in a systematic form was by no means less considerable than that of collecting them. The transactions of scientific societies and the best and latest periodical publications, which have so much multiplied the number of the sources of information, constituted no small part of the collection, which was thus to be reduced into one body of science.

Notwithstanding the comprehensive nature of the lectures or the original ideas they contained, the series of 31 lectures the first year, expanded to 60 the second, was not a great success. It appears that in striving to achieve a balance between rigor and completeness on the one hand and comprehension by a mixed audience on the other, he badly misjudged the general public. This is in contrast to the far more successful but less original lectures of Davy on chemistry given at about the same time.

Young's lectures have achieved a form of immortality granted only a very few. It is in the thirteenth lecture that he introduces the concept of a modulus of elasticity, with which his name is still associated. It must be conceded that even a well-taught mechanical engineer would have difficulty recognizing Young's Modulus of Elasticity as defined in that lecture. The modulus of elasticity of any substance is a column of the same substance, capable of producing a pressure on its base which is to the weight causing a certain degree of compression as the length of the substance to the diminution of its length. In fairness to Young, it must be realized that he was wrestling with the concepts of what we now call stress and strain without the benefit of the contributions of calculus or the great French mathematician Cauchy, who sorted it all out in his 1822

paper for the French Academy of Sciences. The definition of Young's modulus in terms of the slope of the stress-strain curve was actually proposed by Navier in 1826.

In the same lecture Young applies the concept of a stress without naming it to muscle mechanics noting that it is obvious that in muscles of the same kind the strength must be as the number of fibres or as the extent of the surface which would be formed by cutting the muscle across.

In 1802 Young delivered the Bakerian Lecture to the Royal Society. On the Theory of Light and Colours in which he put forward what is in slightly modified form known today as the Young-Helmholtz theory of color vision.

Perhaps his most important contribution was to the theory of light itself which he developed in a series of four papers published during the first four years of the 19th century. Although only 30 at the time these papers represented the culmination of a train of thinking reaching back into his youth. As a boy he was fascinated by optics. His researches for his dissertation in Göttingen were devoted to an attempt to derive a system or alphabet for describing all the sounds which could be formed by the human voice thus forming a basis for an alphabet for all languages. Via his studies on the formation and propagation of sound he began to see analogies with the propagation of light. Building on this base the concepts were expanded during the ample spare time available to him in his Cambridge days and were presented in his 1800 Philosophical Transactions paper entitled 'Outlines of Experiments and Enquiries Respecting Sound and Light'. Unfortunately young Thomas in this paper needlessly took a rather mean swipe at the eminent mathematician and astronomer Dr Smith and one may speculate that in view of later events he would have wished for more self control.

His subsequent three major papers set out with uncommon clarity the basis for the wave theory of light including an unambiguous statement of the principle of superposition of waves leading to interference patterns. In a minor but nonetheless intriguing paper published in 1802 in the Royal Institution Journal under the title 'Harmonic Sliders' he gives details of a simple machine for visually demonstrating the effect of superposition of sine waves coming very close to enunciating what we now call Fourier synthesis. In 1807 with

the publication of his *Course of Lectures on Natural Philosophy* Young essentially rounded off his momentous contribution to the subject.

One would expect that such a profound series of papers on a subject which had been festering unresolved since Newton's efforts would have shaken the world of science causing great excitement. Nothing could be further from the truth. Young was quite simply ignored and the vast majority of active scientists apparently failed to grasp the significance of his work. Even more painful was the vehement attack on his work and his imprudent remarks on Smith by Robinson and subsequently by Brougham. The exchanges were increasingly nasty and founded more on personal dislike than on scientific merit. They achieved their end to inflict pain and to cast doubt upon Young's reputation as a physicist. Even more difficult for him to accept was the prejudicial effect on his medical practice which already was suffering from a certain dilution of attention. In gross oversimplification it was a dark period for Young personally and for the development of the theory of light up until Fresnel's original and powerful support given in 1815-1816. As Wood states in his extensive account of Young's contributions, 'Fresnel must be reckoned as sharing with Young the honour of establishing the wave theory on a broad and sound basis'. In Young's own words 'The theory of light and colours though it did not occupy a large portion of my time I conceived to be of more importance than all that I have ever done or ever shall do besides'.

And what did Thomas Young do with all his spare time during the development of his ideas on light? Among other things he made a contribution which is to this day of significance to the practicing cardiologist. The law of Laplace as we know it today relates the pressure difference across a curved surface to the tensions which must obtain at the surface itself. It constitutes an extremely powerful concept for relating the forces which must be developed by the myocardium to raise the required pressures in the ventricle. Not only is hypertension an excessive load on heart muscle but less obvious and equally true a big heart is a bad heart. Now it so happened that Laplace read his paper on the subject in 1805 and published it in 1806. But on the 24th of December 1804 Young presented his *Essay on the Cohesion of Fluids* to be published in the *Philosophi-*

cal Transactions of 1805 The rival claims of priority by these two giants took some time to be resolved and although there was controversy it was pale by comparison with the debate over the theory of light. In a feeble attempt to redress the matter I personally now refer to the relationship as the Young-LaPlace Law. The supplement to the fourth edition of the *Encyclopaedia Britannica* contains a more fully developed article by Young in which he not only presents the Young-LaPlace Law but also makes the very first estimate of the diameter of a molecule getting within a factor of 100 correct which was pretty good going for the beginning of the 19th century.

Another contribution which may interest the cardiologist was his invention of the kymograph which in the hands of physiologists has revealed most of what we know of the processes of life. A drawing of an elementary form of this device is contained in the plates accompanying the published version of his lectures on natural philosophy.

In the *Philosophical Transactions of 1809* he published the text of his Croonian Lecture before the Royal Society "On the Function of the Heart and Arteries." This together with his paper entitled "Hydraulic investigations subservient to an intended Croonian Lecture on the motion of blood" which appeared in the year before constitute a milestone in cardiovascular mechanics. In the 1808 paper Young gives an analysis of the pressure-flow relations in tubes and was well ahead of his time in describing the scaling laws of such a flow. The relative importance of the square law vs the linear Poiseuille-like term are discussed as a function of dimensions, velocity, viscosity, etc. In fact the essence of scaling with Reynolds number is clearly enunciated roughly 40 years before Osborne Reynolds carried out his crucial experiments.

In the same papers Young analyzes for the first time the nature of pulsating flow in distensible vessels. He derives an expression for the speed of propagation of waves in arteries and gives the method for computing it although once again without calculus and the modern definition of Young's modulus. This formula is couched in rather obscure and impenetrable language. The modern form of this expression is generally referred to as the Moens-Korteweg equation and was presented roughly 70 years later. In a clear

and straightforward line of reasoning Young applies these concepts to deductions concerning the nature of the pulse in various pathological states and with a view to resolving the debate over whether the muscular coat of arteries plays a role of significance in blood flow. He concludes against the operation of the muscular powers of the arteries in the ordinary circulation.

In 1803 after two years of lecturing on natural philosophy embroiled in controversy and concerned with the progress of his medical practice he resigned his professorship at the Royal Institution in the hope of devoting a greater part of his attention to medicine.

In 1811 Young joined the staff of St. George's Hospital and remained happily associated with the hospital until his death 18 years later. He set out to do for the practice of physics what he already had done for physics to set down in a form nearly similar relating to every department of medical knowledge it will be comparatively more concise than these lectures [on natural philosophy] in proportion to what has been said and written respecting physics but I hope much more complete with regard to all that is known with certainty and can be applied with utility. The results of these labors was *An introduction to Medical Literature including a system of Practical Nosology intended as a guide to students and an assistant to practitioners* published in 1813.

In this work the first chapter contains some interesting glimpses of his views on the practice of medicine and on the most appropriate education illustrating his lack of comprehension of the limitations of his less well-endowed fellowmen. I shudder to think what would be the reaction of our students today were we to put into practice his belief that his own lectures on natural philosophy probably contain as much of natural philosophy as is absolutely necessary for a medical student. Once again he was not a popular lecturer badly overestimating his audience.

As near as can be determined it would seem that Young was a competent physician but never succeeded in attaining any real measure of popularity or success. Peacock blames this on Young's approach to patients: gentle and gentlemanly but not genial. Both Wood and Herve support the view of Young's colleague Dr. Brodie who attributes his lack of success to the lack of constant attention to nurturing his practice due

to the demands of his other interests. His practice slowly declined as his interests turned to Egyptology to which he made major contributions and because of his tasks of Secretary of the Board of Longitude and Superintendent of the *Nautical Almanac*.

Sadly very little seems to be known of his private life. In the summer of 1804 he was married to Eliza Maxwell and this relationship would appear to have been quite simply a happy and affectionate one. In 1821 they travelled together to the continent and in the course of this rather grand tour he met with Laplace. In 1827 Thomas Young was elected as Foreign Member of the Academy of Science at Paris succeeding to the chair left by the death of Volta earlier that year.

Early in 1829 Young began to suffer from repeated attacks of asthma and general weakness. He managed to muster the strength to continue attendance at the Council meetings of the Royal Society, his last being the 26th of March 1829. In bed he struggled with pencil for he could no longer hold a pen fast to complete his *Rudiments of an Egyptian Dictionary*.

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Clinical communications

Heart rate levels and ventricular ectopic activity during cardiac rehabilitation

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In many centers exercise programs have been developed for rehabilitation of patients after a myocardial infarction. It has been recommended that candidates for participation should be screened in order to evaluate their motivation to eliminate undue risk and to evaluate the possible benefits of the program. In particular several authors state that patients with frequent multi-form or repetitive premature ventricular complexes (PVCs) should not be accepted for physical training unless the arrhythmia has been treated. However in spite of the widespread experience with rehabilitation of cardiac patients little information is available on the actual incidence of arrhythmias during rehabilitation programs. In one study heart rates and arrhythmias have been described during exercise tests and ambulatory monitoring including cardiac exercise classes. However no separation was made between data during the exercise period and during other activities. The present study was designed to address the following questions:

1 Which heart rate levels are reached during rehabilitation of groups of patients with coronary artery disease?

2 How are these heart rates related to those during a symptom limited exercise test and during normal daily activities?

3 Which patterns of ventricular ectopic activity occur during the rehabilitation program?

4 Can these arrhythmias be predicted from either the exercise test or ambulatory monitoring during normal daily life?

Patient selection

Data were analyzed from 40 patients with coronary artery disease: there were 39 males and one female between 32 and 65 years old. Three other patients had to be excluded due to failure of the ambulatory ECG tape recording. Thirty-six patients were enrolled in the rehabilitation program after a myocardial infarction. The interval between the infarction and the study was 3 to 8 months in six patients, 7 to 12 months in 11 patients, and 1 to 3 years in the remaining 19 patients. Three patients were studied between 3 and 6 months after coronary bypass surgery. Finally one patient was admitted to the program because of moderate angina pectoris. At the time of the study patients had participated in the rehabilitation program between 1 and 6 months. In Rotterdam patients can be referred to the rehabilitation program from several major hospitals and by private physicians. In general medical therapy is provided by the referring physician. Therefore indications for antiarrhythmic therapy and other drugs may vary between the participants in the rehabilitation program. Actually 14 patients used no medication except anticoagulants or nitroglycerin. Seventeen patients were on beta blockers, seven used antiarrhythmic drugs, six took digoxin, and five patients received seda-

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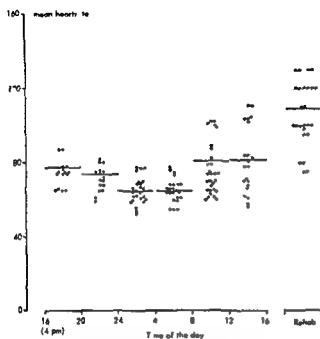


Fig 2 Distribution of the mean heart rates measured over a 4 hour period with those during rehabilitation. The horizontal line in each column represents the mean value

Table III Ventricular arrhythmias during rehabilitation*

| PVCs | No. of patients |
|--------------|-----------------|
| 0 nil | 17 |
| 1 <5/minute | 14 |
| 2 ≥5/minute | 1 |
| 3 multiform | 2 |
| 4 repetitive | 6 |

*Most were type of PVC during the rehabilitation period in each individual.

The ECGs were analyzed at high speed by trained technicians using the Medilog system (Oxford Instruments). The 24 hours preceding the training and the actual training period were analyzed separately.

A symptom limited exercise test was performed within the same week. Medication was not changed during this period. Workload on a calibrated bicycle ergometer was increased with steps of 10 Watts per minute until near exhaustion (moderate angina pectoris or dyspnea). Three ECG leads were continuously recorded on paper with paper speeds of 10 and 25 mm per second alternately.

Premature ventricular complexes were classified as shown in Table I. The part of the 24 hour

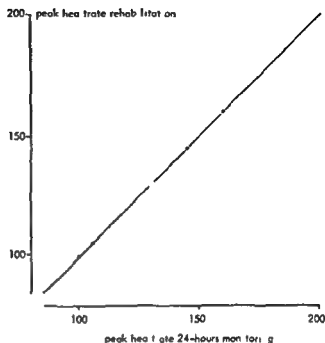


Fig 3 Comparison of the peak heart rate during rehabilitation with the highest heart rate during the preceding 24 hours.

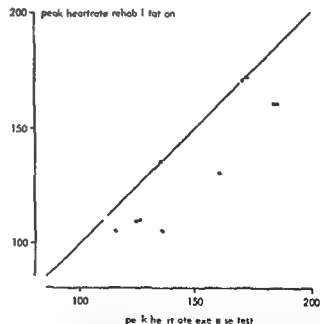


Fig 4 Comparison of the peak heart rate during rehabilitation with the highest heart rate achieved during a symptom limited graded exercise test within the same week.

recording during which each type of arrhythmia occurred was indicated semiquantitatively in five classes as shown in Table II: absent (occasional (less than 2 hours of ECG recording), episodic (2 to 12 hours), frequent (12 to 22 hours), and

EXERCISE TEST

| | 0 | 1 | 2 | 3 | 4 |
|-----|----|---|---|---|---|
| 0 | 12 | 5 | | | |
| R 1 | 2 | 8 | 2 | 1 | 1 |
| E 2 | | | | | 1 |
| A 3 | | 2 | | | |
| B 4 | 2 | 1 | | | 3 |

Fig 5 Most severe grade of PVC (see Tables II and III) in each patient during the rehabilitation program (REHAB) compared with the highest grade of PVC during the exercise test. The dotted lines separate patients with severe PVCs grades 2 to 4 from those with less than five PVCs per minute or without PVCs.

continuous (22 to 24 hours). Heart rates were measured from trend plots as shown in Fig 1. The mean heart rate was measured every hour as well as the highest heart rates reached during 24 hours and during rehabilitation.

Results

In Fig 2 the heart rates during the 24 hours preceding rehabilitation are compared with the mean heart rates during rehabilitation. In 37 patients the mean heart rate during rehabilitation was higher than the heart rate during any hour of the preceding day and night. In addition the peak heart rates during rehabilitation exceeded those during 24 hour recording in 33 out of 40 patients as illustrated in Fig 3.

With the rehabilitation session peak heart rates were found during jogging in 20 patients and during volleyball in the remaining 15 patients. These data indicate that most patients exercised more vigorously during the rehabilitation program than at any moment of their normal activities. However, even during rehabilitation many patients did not reach the same heart rate level as during the exercise test which was performed within the same week. The peak heart rates

24 HOUR MONITORING

| | 0 | 1 | 2 | 3 | 4 |
|-----|---|---|---|---|---|
| 0 | 6 | 8 | | 2 | 1 |
| R 1 | | 6 | | 5 | 3 |
| E 2 | | | | | 1 |
| A 3 | | | | 1 | 1 |
| B 4 | | | | 1 | 5 |

Fig 6 Most severe grade of PVC (see Fig 5) in each patient during the rehabilitation program (REHAB) compared with the highest grade of PVC during 24 hours of normal daily activities.

during the exercise test exceeded those during rehabilitation by 10 beats or more in 20 patients (Fig 4) while in five patients the peak heart rate during rehabilitation was 10 beats higher during rehabilitation than the heart rate during the exercise test.

The performance during the exercise test averaged 92% (SD = 15%) of the predicted normal values. Peak heart rates in those patients without beta blocker therapy averaged 89% (SD = 12%) of the age predicted maximum heart rate in each patient.

The premature ventricular complexes observed during the symptom limited exercise test are presented in Table I. PVCs occurred during all stages of the test. Repetitive PVCs (code 4) were only observed during the highest workload and in the recovery period. The occurrence of PVCs during 24 hours of normal daily activity are given in Table II. In most patients PVCs were observed occasionally. In six patients frequent PVCs were present. The incidence of premature ventricular complexes during the symptom limited exercise test was similar to the results of other investigators. In 22 out of 40 patients the PVCs during the stress test were of lower grade than those during 24 hours of ambulatory monitoring. This again is in agreement with data published by

others.¹¹⁻¹³ In two patients however a higher grade of PVC occurred during the exercise test. Apparently these two methods disclose different information regarding the electrophysiological state of the myocardium.¹⁴

The distribution of PVC during the rehabilitation session is shown in Table III. In Figs. 5 and 6 the data in each patient are compared under the three different conditions: exercise test, normal activities and rehabilitation program. It is shown that the PVCs during rehabilitation could not be predicted from the exercise ECG. The sensitivity for prediction of severe PVCs (grades 2 to 4) during rehabilitation from the exercise test is only 44% (four out of nine cases) while the specificity is 87% (27 out of 31 cases) as shown in Fig. 5. On the other hand all nine patients with severe PVCs during rehabilitation were detected by ambulatory ECG recording (sensitivity 100%) at the cost of a poor specificity (20 out of 31 = 64%) as presented in Fig. 6. No differences in ventricular ectopic activity were observed between the patients who took digitalis, beta blockers or other antiarrhythmic drugs.

Discussion

In the Rotterdam Rehabilitation Program patients are exercised in groups under medical supervision but without ECG monitoring. The program consists of jogging, walking, calisthenics and ball games. Many patients were able to perform in the program at similar levels of work as in the symptom limited exercise test on the bicycle ergometer (Fig. 2). Most patients reached considerably higher heart rates during rehabilitation than during their other activities. The occurrence of ventricular arrhythmias was not related to the level of physical activity as represented by the heart rate. Most PVCs were observed during normal activities and fewer during the exercise test and during the rehabilitation program. This may be due to the length of the ECG records since the majority of arrhythmias occurred during less than 2 out of 24 hour monitoring period (Table II) while the exercise test and the rehabilitation program had a duration of approximately 30 and 60 minutes respectively.

It has been recommended that patients with frequent multifocal or repetitive PVCs should not be accepted in a rehabilitation program. However neither the exercise test nor ambulatory monitoring provided an accurate prediction of

the type of PVC seen during the rehabilitation program. Five patients had multifocal or repetitive PVCs during rehabilitation while no PVC or less than 1/minute occurred during stress testing (Fig. 4). Thus the sensitivity of exercise tests for the prediction of higher grade PVCs during rehabilitation is low. Ambulatory monitoring predicted all patients with PVCs during rehabilitation. However it would be impractical to exclude patients with frequent multifocal or repetitive PVCs on the 24 hour recording from a rehabilitation program since these arrhythmias occur in many post infarct patients at some time or other. In fact in the present series 20 out of 40 patients should have been excluded according to such a criterion while only nine of these 20 developed grade 2 to 4 arrhythmias during the actual rehabilitation session (Fig. 6). Since it appeared to be impossible to predict PVCs during rehabilitation from either the exercise ECG or the ambulatory tape recording we conclude that exclusion of patients from the rehabilitation program should not be based on the observation of higher grade PVCs per se. It is likely that the risk of cardiac arrest or other cardiovascular incidents is greatest in those patients with extensive left ventricular impairment especially in those with a low physical capacity and with an inadequate heart rate or blood pressure response during exercise.¹⁵ Selection of patients by such criteria seems more appropriate than exclusion of all those patients who show higher grade arrhythmias during an exercise test.

In the present investigation no life threatening arrhythmias occurred. During our total experience of 5 years of cardiac rehabilitation in Rotterdam which involved 15 000 patient hours one patient developed ventricular fibrillation. This patient was successfully resuscitated and subsequently underwent coronary bypass surgery. An excess mortality was reported in a recent review by Haskell¹⁶ which covered 30 cardiac rehabilitation programs in the USA and Canada. During more than 1 600 000 hours of supervised exercise 50 cardiac arrests were reported, eight of which were fatal. In addition five non-fatal and four other fatal cardiovascular accidents and exclusion of seven deaths in cardiac rehabilitation programs in a small group of patients the mortality rate was 1 per 100 000 patient hours which corresponds to an annual mortality rate of 0.36%.

41%. It should be noted however that 42 patients with cardiac arrests were successfully defibrillated. This indicates that the risk of cardiac arrest during rehabilitation is considerably higher than the risk during other activities in spite of the selection criteria which were applied by the various centers. Therefore promotion of exercise programs for patients with coronary artery disease should be avoided unless the experienced personnel and appropriate equipment are immediately available. This risk of cardiac rehabilitation can be covered effectively by personnel who have been trained in cardiopulmonary resuscitation.

Summary

The heart rate levels and the incidence and types of premature ventricular complexes (PVCs) during the rehabilitation of 40 patients with coronary artery disease were compared with those during 24 hour ambulatory monitoring and during a symptom limited exercise test. Thirty six patients were studied 3 months or later after a myocardial infarction and four patients were studied after coronary bypass surgery. The last patient suffered from moderate angina pectoris. Peak heart rates during rehabilitation exceeded those during other activities in 34 out of 40 patients. Half of the patients reached even higher heart rate levels during the exercise test. Twenty three patients had PVC during rehabilitation; frequent multiform or repetitive PVC occurred in nine of these. During the exercise test 24 patients had PVCs while PVCs were observed on the ambulatory tape recording in 34 patients. Frequent multiform and repetitive PVCs occurred in eight patients during exercise testing and in 20 patients during monitoring. No relation was found between either the incidence or the type of PVC in individual patients under these three conditions. Thus selection of patients with a high risk for arrhythmias during rehabilitation is not feasible by either exercise testing or ambulatory tape recording.

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Tocainide therapy for refractory ventricular arrhythmias

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Parenteral lidocaine is particularly effective in the acute control of ventricular ectopy in the early post myocardial infarction period. However, chronic oral therapy has not proven feasible in part because of a short half life of elimination. In addition, lidocaine undergoes extensive first pass hepatic extraction¹ leading to accumulation of the de-ethylated metabolites, monoethylglycinexylidide (MEGX) and glycinexylidide (GX), these contribute to side effects during oral therapy.² Tocainide is a congener of lidocaine (Fig 1) which has been shown to have antiarrhythmic efficacy in man³ when given orally. It is particularly suitable for long term use since absorption after oral administration is virtually complete and its long half life of elimination (12 to 22

hours) allows dosing on an eight to 12 hourly basis. We report our experience with the use of tocainide in a group of patients whose complex ventricular arrhythmias could not be successfully treated with the standard therapeutic regimens.

Materials and methods

Patients were studied in the coronary care unit or the Clinical Research Center of Vanderbilt University Hospital. All those who had received trials of quinidine, procainamide, propranolol and disopyramide without satisfactory response were candidates for this trial. Plasma concentrations of quinidine, procainamide and propranolol were routinely monitored. These agents were considered ineffective if

- 1 Computerized analysis of 12 to 24 hours of ECG documented lack of sustained (>60%) arrhythmia suppression and persistence of symptoms with plasma concentrations in the range usually associated with efficacy, or

- 2 Acute intravenous or oral dosing with computerized analysis of ECG data pre and post therapy showed no change in the arrhythmia with the attainment of plasma concentrations in the usual therapeutic range, or

- 3 Patients developed intolerable side effects with lack of suppression of their arrhythmia at lower dosages, or

- 4 Patients developed allergic or immunologic side effects which necessitated the discontinuation of therapy, or

- 5 Therapy with a given agent was contraindicated.

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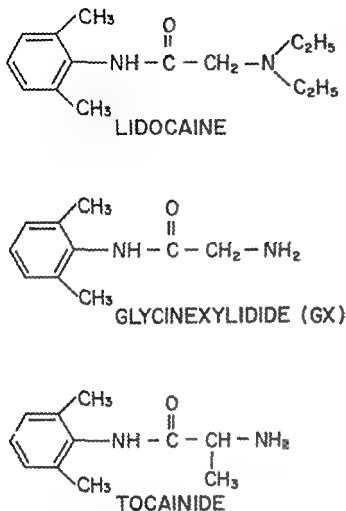


Fig 1 Chemical structures of lidocaine, glycinexylidide, a lidocaine metabolite, and tocainide

Lidocaine responsiveness was assessed in all patients. This was done either by (1) a loading infusion at 120 $\mu\text{g}/\text{Kg}/\text{minute}$ for 25 minutes (15 patients) or (2) the assessment of lidocaine responsiveness by the review of rhythm strips and charts after standard acute therapy in a CCU setting most often 100 to 150 mg intravenously followed by an infusion of 1 to 4 mg/minute (four patients). Arrhythmias were considered responsive to lidocaine if 90% or more ventricular ectopic depolarizations (VEDs) and all complex arrhythmias were abolished without symptoms. Such strict criteria were necessary because of the short control periods used. Plasma concentrations when available were monitored with either approach.

Patients with symptomatic arrhythmias resistant to standard therapy (as described above) regardless of lidocaine response were asked to participate in the evaluation of the use of tocainide for control of refractory ventricular arrhythmias.

Patients giving informed consent were then withdrawn from other antiarrhythmic therapy (usually lidocaine) if possible. After 24 to 48 hours of ECG recording while receiving placebo, tocainide was begun at low dosages (200 to 400 mg orally every 8 to 12 hours). Each dosage level was continued until steady state was achieved (36 to 48 hours) at which time 12-hour ECG tapes and plasma for trough tocainide concentration were obtained and the daily dosage was increased if necessary. The dosage was increased to the point of arrhythmia suppression or the development of side effects. Transient dose-related side effects were controlled if possible by the adoption of lower doses at shorter dosing intervals or by the administration of medication with a meal or snack.

In this highly selected group of patients, chronic oral therapy with tocainide or the conventional agents described above was declared successful if a 60% decrease in VED frequency was documented as well as suppression of symptomatic ventricular tachycardia (VT) while the patient was ambulatory in hospital. In order to avoid misinterpreting spontaneous variation in arrhythmia frequency for a drug response, comparisons were made between pre-drug placebo control data and all dosages of tocainide to ascertain if a dose-response relationship was present. As well, therapy with tocainide was discontinued after the trial to detect a return to baseline arrhythmia frequency and severity in those who appeared to respond; this was omitted in patients whose clinical status was felt to be too unstable to permit such a maneuver.

ECG data were recorded on eight-track tape using a Honeywell model 96 FM recorder. Tapes were then analyzed by a blinded computer operator using a PDP 11/40 laboratory minicomputer and a previously described and verified program which counts VEDs and runs of VT (≥ 3 VEDs in a row rate $\geq 100/\text{minute}$) using a template matching algorithm.

Patients whose arrhythmia was responsive to tocainide were discharged on the dosage regimen providing maximum benefit and a minimum of side effects and were followed as outpatients at weekly to monthly intervals. Routine electrocardiograms, hematology (Coulter counter), biochemistry (SMAC), and antinuclear antibody (ANA) tests (Meloy Kit 6715 Electronic Drive, Springfield, VA) were performed at each visit.

Table 1 Study population

| | Age | Sex | Type of heart disease | Character of arrhythmia | Symptoms at the time of trial |
|---------------------------------|-----|-----|-----------------------|-------------------------|-------------------------------|
| Tocainide responsive | | | | | |
| 1 | 46 | M | ASCVD | VT VF | Syncope CHF |
| 2 | 41 | F | Unknown | VT | Syncope stroke |
| 3 | 30 | F | MVP | VT | Syncope |
| 4 | 69 | F | ASCVD | VT | Syncope CHF |
| 5 | 41 | F | Cardiomyopathy | VT | DOE |
| 6 | 60 | F | ASCVD | VT | Syncope |
| 7 | 59 | M | Unknown | VT | Syncope |
| 8 | 69 | F | ASCVD | VT VF | Syncope |
| 9 | 52 | F | HHD | VEDs | Palpitations, DOE |
| 10 | 60 | F | Unknown | VEDs | Palpitations |
| 11 | 57 | M | ASCVD | VEDs | Angina CHF |
| 12 | 54 | F | MVP | VEDs rare VT | Syncope |
| 13 | 47 | M | ASCVD | VT VF | Syncope CHF |
| 14 | 35 | M | Cardiomyopathy | VT VF | Syncope CHF |
| 15 | 60 | M | ASCVD | VT | Near syncope CHF |
| Tocainide non responsive | | | | | |
| 1 | 32 | F | Unknown | VT | Syncope |
| 2 | 51 | M | ASCVD | VT | Palpitations |
| 3 | 28 | F | Unknown | VT | Syncope stroke |
| 4 | 35 | F | Unknown | VT | Syncope |

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; MVP = mitral valve prolapse; VT = ventricular tachycardia; VF = ventricular fibrillation; VED = ventricular ectopic depolarization; DOE = dyspnea on exertion; CHF = congestive heart failure; HHD = hypertensive heart disease.

Emergency DC-cardioversion required in the past

Rhythm control was evaluated by 30 to 120 minute rhythm strips run at 10 mm/sec by periodic 24 hour Holter recording and by the presence or absence of symptoms of VT.

Blood samples for determination of plasma tocainide concentration were obtained in the 30 minutes prior to a dose and 60 to 90 minutes after a dose for the assessment of plasma concentrations associated with therapeutic effects and with possible adverse effects. Following the addition of glycinylidide as an internal standard plasma was extracted into methylene chloride at an alkaline pH. Aliquots were then injected into a μ Bondapak C column (3.9 x 300 mm). The analysis used a high performance liquid chromatograph (Waters Associates Milford Mass.) the flow rate of the mobile phase (water: methanol: acetic acid (500:100:15 (v/v/v))) was 1.5 ml/minute at ambient temperature. Eluate was monitored for UV absorption at 254 nm (spectrophotometer model 440 Waters Associates). Samples of drug free plasma to which internal standard and varying amounts (0 to 15 μ g/ml) of tocainide had been added were used to prepare a standard curve relating peak height ratio (tocainide inter-

nal standard) to tocainide concentration. Peak height ratios from patient samples were then used to determine tocainide concentration. The coefficient of variation was 8.9 to 9.6% for concentrations ≥ 10 μ g/ml. At lower concentrations (≤ 5 μ g/ml) it rose to 21 to 23%. The sensitivity of this method allowed detection of concentrations of tocainide $\geq .5$ μ g/ml. Samples from patients being treated with quindine, procainamide, disopyramide, phenytoin, propranolol, digoxin, warfarin, hydrochlorothiazide, furosemide, diazepam, flurazepam, aspirin and acetaminophen produced no interfering peaks. Data from patients who had received lidocaine within the previous 24 hours were not used because of potential interference by GX.

Results

Nineteen patients participated in this study (Table I). The ages ranged from 28 to 69 years. 12 were female. Eight had coronary artery disease, one had hypertensive heart disease, two had mitral valve prolapse and two had congestive cardiomyopathies; the remaining six had ventricular arrhythmias with no identifiable heart dis-

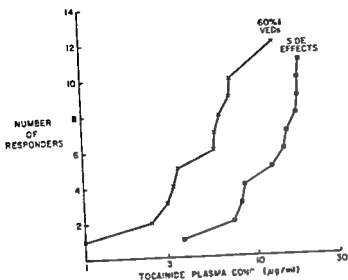


Fig 2 Relationships between the cumulative number of patients demonstrating a response (arrhythmia suppression or side effects) and tocainide concentration

ease All six had normal echocardiograms QTc intervals (range 360 to 420 msec) and physical examinations Follow up ranged from 2 to 15 years and neither congestive heart failure nor angina developed in any patient Symptoms in the 19 patients ranged from palpitations to syncope cerebrovascular accidents and cardiopulmonary arrests All had frequent VEDs Fifteen had a history of ventricular tachycardia and four of these had previously documented ventricular fibrillation

Fifteen of the 19 responded to tocainide (as defined above) All 13 patients whose arrhythmia was sensitive to lidocaine were in this group while only two of the six patients resistant to lidocaine responded to tocainide ($P < 0.005$ Fisher's exact test) Lidocaine resistance was documented in four patients by the absence of change in arrhythmia frequency and by the presence of typical side effects during the infusion protocol after a mean dose of 270 mg (range 180 to 390 mg) over 25 minutes The fifth patient had no change in arrhythmia frequency and a plasma concentration of 5.8 µg/ml following the lidocaine infusion and the sixth patient was judged lidocaine resistant following review of her CCU data showing no change in arrhythmia frequency during prolonged infusions of 2 to 3 mg/minute

Dose response plots relating reduction in VED frequency (from placebo baseline) to trough tocainide concentration (at steady state) could be constructed in 12 (patients 1 to 12) responders

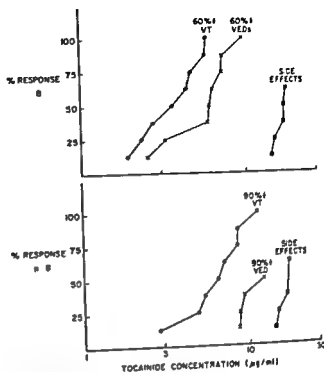


Fig 3 Dose-response relationships for VED suppression, VT suppression, and side effects among the eight patients with frequent VT

Placebo baseline recordings were not obtained in the other three (patients 13 to 15) but tocainide was effective in abolishing their frequent runs of symptomatic VT All of these 12 patients demonstrated incremental reductions in VED frequency as the plasma concentration of tocainide increased The plot relating plasma concentration to aggregate response in the group is shown in Fig 2 a curve relating concentration to the observed incidence of side effects (see below) for the entire group of 19 patients is also shown in Fig 2 Eight of these twelve (patients 1 to 8) had frequent runs of VT (≥ 2 episodes per hour) during placebo therapy Fig 3 shows the relationship among VED reduction, VT reduction, and side effects in this group

Return of arrhythmia to $88\% (\pm SE 18)$ of placebo control frequency was observed in 11 of the 15 responding patients (Fig 4) This maneuver was not attempted in three (patients 8, 13, 14) and in a fourth (patient 6) VT recurred only hours after she missed a dose of tocainide necessitating reinstitution of therapy Concurrent antiarrhythmic therapy was undertaken in two patients In one a partial response to tocainide was seen initially and a greater degree of arrhythmia control was established with the addition of

procainamide. This patient had had no response to procainamide alone and so was discharged on the two agents together; he subsequently died (see below). A second patient underwent tocainide dose ranging while receiving propranolol for paroxysmal atrial tachycardia. She developed tremor and nausea and was not judged to have an antiarrhythmic response to tocainide. Four patients were also treated with digoxin, three for control of congestive heart failure and one for paroxysmal atrial fibrillation.

Side effects were observed in 11 patients (58%) during tocainide therapy and most often occurred immediately following a dose taken on an empty stomach. These side effects affected primarily the central nervous system (ataxia, paresthesias, lightheadedness, nervousness and tremor); the other dose-related side effects were gastrointestinal (primarily nausea). In four patients the margin between effective and excessive plasma concentrations was so narrow that outpatient treatment had to be stopped.

Chronic outpatient therapy with tocainide was undertaken in 12 of the 15 responders; three could not be discharged on drug (two developed drug allergy in hospital and one died). The discharge regimens were 800 to 2400 mg/day (mean 1600) in two to three divided doses. Three additional deaths have occurred (see below); four patients have had to stop therapy because of prominent central nervous system side effects at effective antiarrhythmic dosages and three further cases of drug allergy have occurred. Maintenance of arrhythmia control was documented at the regularly scheduled clinic visits in all patients (including those who subsequently died); symptoms previously related to the arrhythmia did not recur. Two (patients 1 and 8) continue on treatment and are asymptomatic at one and four years respectively. Drug withdrawal and substitution of placebo has been carried out three times over the 4 years; patient 1 has been on treatment on each occasion; return of ventricular tachycardia was documented.

Four patients died during tocainide therapy. One was a 35-year-old man with a congestive cardiomyopathy who died in hospital after the initial trial of tocainide; his symptomatic runs of VT were suppressed with treatment, leaving isolated VEDs and couplets. He died in cardiogenic shock while awaiting heart transplantation.

The second patient was a 47-year-old man with

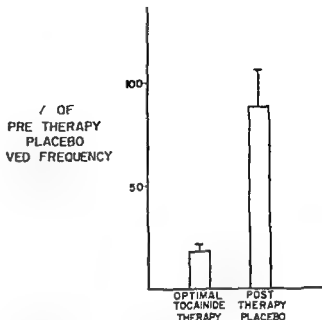


Fig. 4 Comparison of VED frequency at the end of tocainide dose ranging and following tocainide withdrawal (mean \pm SE).

severe coronary artery disease and recurrent ventricular fibrillation initially controlled on tocainide. Two weeks after discharge on tocainide he developed atrial tachycardia followed shortly by ventricular fibrillation that required DC cardioversion and was eventually controlled with a combination of procainamide and tocainide. After a total of 3 months on tocainide while at home he developed increasing symptoms of congestive heart failure and had another cardiopulmonary arrest. He was taken to his local hospital where ventricular fibrillation was documented and he could not be resuscitated. Postmortem tocainide plasma concentration was in his usual therapeutic range (100 μ g/ml) but procainamide (114 μ g/ml) and N-acetylprocainamide (199 μ g/ml) were well above his usual levels.

The third patient who died was a 52-year-old woman who died suddenly at home after 5 months of therapy. She had been seen in the clinic four days before with tocainide levels in her usual range and good arrhythmia control but had stopped taking her medications the day prior to her sudden death.

The fourth patient was a 57-year-old man with coronary artery disease and congestive heart failure. He had been receiving tocainide for 13 months. After developing increased angina and dyspnea at home he died suddenly; autopsy

showed a coronary artery dissection which was thought to have precipitated a fatal arrhythmia. Tocainide concentration was 109 $\mu\text{g/ml}$ post mortem.

Five patients developed allergic symptoms during tocainide therapy. In four these occurred within six weeks of the initial dose while a rash developed in the fifth after four months on therapy. Two patients had pruritic rashes only, one patient had pruritus without a rash, a fourth had rash, pruritus, night sweats and eosinophilia and the fifth had fever and night sweats. All symptoms resolved promptly with withdrawal of tocainide and in no case could other agents be implicated as a possible cause.

Biochemical and hematological screening tests showed no adverse reactions during tocainide therapy. One patient entered the trial with a strongly positive ANA test which had developed during procainamide therapy over the previous 8 months; she was symptomatic with arthritis and pulmonary infiltrates. The ANA have persisted during the year she has been taking tocainide although the symptoms and infiltrate have resolved. Two other patients developed ANA shortly after starting tocainide but in both cases prior procainamide therapy could be implicated and in neither did symptoms of lupus erythematosus develop.

Discussion

There is evidence that chronic therapy with beta blocking agents, anti platelet agents, or phenytoin might reduce the incidence of sudden death in a high risk population. Procainamide and quinidine have been studied by Myerburg and colleagues in survivors of ventricular fibrillation; maintenance of serum levels in the therapeutic range appeared to be the major determinant of the incidence of recurrent fibrillation rather than isolated VED frequency. The high incidence of side effects during therapy with these agents and the question of what defines a "therapeutic" concentration in this context have not yet been addressed. One possibility is that while VEDs may be unchanged during adequate therapy, more complex arrhythmias may be disproportionately decreased. A tendency toward such a reduction was seen in the study of Myerburg and associates although statistical significance was not achieved. We have recently shown that a 70% decrease in VED frequency during

propranolol therapy was associated with abolition of VT.¹¹ The similar disproportionate reduction in VT frequency as plasma concentration increased that we have now demonstrated with tocainide suggests that this phenomenon may occur often.

The definition of the therapeutic window, i.e., the range defined by plasma concentrations associated with effective and with excessive drug actions is arbitrary. The degree of acceptable risk of side effects varies among individuals (and populations) as does the end point used to designate response (Fig 3). In this study group 20% of the 19 patients developed side effects at plasma tocainide concentrations $\geq 11 \mu\text{g/ml}$, while 20% of those responding (with $\geq 60\%$ VED suppression) did so at plasma concentrations $\geq 3 \mu\text{g/ml}$ (Fig 2). Thus using arbitrary 20% limits on acceptable degrees of efficacy and toxicity the range 3 to 11 $\mu\text{g/ml}$ could be termed the therapeutic window for tocainide in this group.

Recent observations have increased awareness of the problem of spontaneous variation in VED frequency. Morganroth and colleagues¹ advocated use of prolonged recordings of ECG data during control and drug periods to avoid misinterpreting this spontaneous variation. Virtual abolition of arrhythmias is needed to demonstrate efficacy with short periods of observation such as acute response to lidocaine.¹² However, lesser changes in arrhythmia frequency may be attributed to drug treatment if longer periods of observation are undertaken. The prolonged periods of observation used in this study as well as the demonstration of dose response relationships showed that tocainide had antiarrhythmic activity in these patients. Re-emergence of arrhythmias during substitution of placebo for active therapy provided additional evidence that this was a true drug effect. In the three patients in whom tocainide was not withdrawn the dramatic clinical improvement (no further cardiac arrests) during tocainide dose ranging as well as increasing VED suppression made it unlikely that the observed response was fortuitous.

Acute sequential drug testing has been proposed as an approach to the patient with serious symptomatic arrhythmias.¹³ However translation of the results of acute drug testing to chronic oral therapy is not always possible. For instance testing with intravenous propranolol for VED suppression does not predict response to oral

therapy " Acute drug testing does not permit accumulation of metabolites which may have antiarrhythmic activity of their own response to procainamide challenge does not predict subsequent response to N acetylprocainamide " We have now shown that response to acute challenge with one agent lidocaine predicts response to a different (although structurally related) agent tocainide in patients whose arrhythmias are not controlled by conventional oral drug therapy The fact that the spectrum of side effects seen during the use of these two agents is also similar may reflect the structural similarity among lidocaine its metabolites and tocainide

Trials of tocainide in populations of patients who did not exhibit the resistance to standard agents shown by this group have had a 66 to 71% response rate^{1, 17} Winkle and colleagues¹⁸ and Ryan and associates¹⁹ have reported their experience with patients resistant to conventional therapy the initial response rates were also 70% Three of the 17 patients reported by Winkle and colleagues died on therapy No deaths were recorded among those treated with tocainide by Ryan and co workers although that group also noted a high incidence (70%) of dose related symptoms and two cases of drug related rash (6.7%)^{1, 19}

The high mortality rate in this and other reports of chronic tocainide therapy reflects the underlying severity of the rhythm disturbance and basic disease process among these highly selected groups of patients It may also be that reduction in VED (or VT) frequency does not decrease the risk for sudden death despite an association between the two However even during short periods of therapy these highly selected patients often note improvement in other VED related symptoms such as dyspnea on exertion or recurrent syncope In such patients the only clinically attainable end point may be suppression of symptoms even after systematic trials of multiple conventional and investigational agents¹

Trials of new antiarrhythmic agents in this setting are biased by the referral and selection processes The true place of tocainide in the therapy of ventricular arrhythmias and sudden death prophylaxis is not yet known It provided long term life saving treatment in two of our 19 patients In this population of patients with resistant arrhythmias the use of tocainide was

associated with a good initial response rate but a narrow toxic therapeutic ratio and a high incidence of drug allergy which limited therapy in many patients

Summary

Tocainide a congener of lidocaine was used to treat symptomatic ventricular arrhythmias in 19 patients resistant to or unable to tolerate conventional agents In this highly selected group 15 showed good initial responses to oral therapy Ventricular tachycardia was suppressed to a greater extent than isolated ventricular ectopic depolarizations at any plasma concentration and upward dose ranging showed progressive suppression of both Arrhythmia responsiveness to lidocaine was found to be an excellent predictor of tocainide response

Of the 15 responders one died 24 hours after stopping therapy three died while receiving tocainide nine stopped because of adverse reactions (five allergic) and two continue on therapy at 1 and 4 years We conclude that tocainide is an effective agent for the short term suppression of ventricular arrhythmias particularly ventricular tachycardia sensitive to lidocaine but a high incidence of adverse effects limits its application to chronic therapy in many patients

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The electrophysiologic effects of intravenous lidocaine in the Wolff-Parkinson-White syndrome

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In spite of the progress in our understanding of the pathophysiology of the Wolff-Parkinson-White syndrome since its description in 1930,¹ knowledge of the most appropriate medical therapy is still inadequate. Clinically, it is difficult to assess therapy in the Wolff-Parkinson-White syndrome as the tachycardias are variable and paroxysmal,¹ and because patients may historically overstate or understate the incidence of palpitations.²⁻⁴ Knowledge is accumulating, however, with the increasing number of electrophysiologic assessments of the effects of therapy in this syndrome.⁵⁻⁸

Isolated clinical case reports¹ have indicated that intravenous lidocaine may be effective therapy for supraventricular tachyarrhythmias with accessory pathway conduction. Lidocaine in fact has been reported as being extremely valuable^{1,2} in this regard because of a depressant effect on accessory pathway conduction. Such supraventricular tachyarrhythmias may resemble ventricular tachyarrhythmias which may also occur in the WPW syndrome^{3,4} and lidocaine is known to be effective therapy for these.⁵ Accordingly, in an acute situation differentiation between supraventricular tachyarrhythmias with accessory pathway conduction

and ventricular tachyarrhythmias may be academic. The purpose of this study, therefore, was to obtain an electrophysiologic assessment of lidocaine in the WPW syndrome.

Material

Twelve patients with the WPW syndrome were studied. One had coronary heart disease and another had Ebstein's anomaly. There were 10 males. The ages of the patients ranged from 15 to 63 years with a mean of 33 ± 5 years (mean \pm standard error of the mean). Seven patients had Type A¹ WPW syndrome and in one of these the WPW anomaly was intermittent. Five patients had Type B¹ WPW syndrome. Tachycardia had been present in all patients for a mean of 11 ± 3 years with a mean frequency of approximately monthly occurrence.

Methods

The studies were performed in the fasting state after obtaining informed consent. The patients had not received any medication for at least 48 hours prior to study. Intracardiac electrograms were obtained by standard techniques¹¹ and were recorded on a multichannel photographic recorder with paper speeds between 25 and 100 mm/sec (Electronics for Medicine Model DR 12). Multiple standard electrocardiographic leads were recorded with high right atrial, low right atrial, coronary sinus, and His bundle electrograms. The protocol used was as previously described.¹²⁻¹⁴

During sinus rhythm the heart rate and P-delta, AH, and HV intervals were measured. High right atrial pacing¹ was performed at

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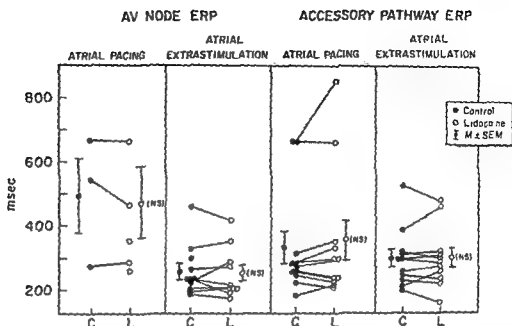


Fig 1 Anterograde AV effective refractory period (ERP) of the AV node and the accessory pathway as determined by the atrial pacing and extrastimulus techniques. Statistical analysis (NS = no significant change) relates only to those cases where determinations were able to be made in both the control state (C) and after lidocaine (L). Results are expressed as mean \pm standard error of the mean.

rates to assess anterograde AV refractoriness. A measurement of anterograde AV node effective refractory period was obtained by taking the cycle length of the maximum rate of atrial pacing where 1:1 AV node conduction was preserved. The anterograde accessory pathway effective refractory period was taken as the cycle length of the maximum rate of atrial pacing where 1:1 accessory pathway conduction was preserved. The atrial extra stimulus technique^{15, 16} during atrial pacing was used to determine the anterograde AV node and accessory pathway effective refractory periods and the atrial muscle effective refractory period. Right ventricular apical pacing was performed at increasing rates to assess ventriculoatrial (VA) conduction. The VA conduction time was measured from the ventricular stimulus artifact to the onset of the right septal atrial, coronary sinus and high right atrial electrograms. A measurement of the VA effective refractory period was taken as the cycle length of the maximum rate of ventricular pacing where 1:1 VA conduction was preserved. The ventricular extra stimulus technique during ventricular pacing was used to determine the VA and the ventricular muscle effective refractory periods.

The initiation of tachycardia by these maneuvers^{18, 40} was noted. The rate and VA conduction time in the case of reentry tachycardia and the

shortest RR interval of the ventricular response in the case of atrial fibrillation were measured.

The above procedures were repeated with the catheters in the same positions after an intravenous bolus of lidocaine 1 mg/kg administered over 30 seconds. The repeat studies begun 1 minute after the bolus were completed in all patients within 15 minutes. Statistical evaluation was performed with Student's *t* test for paired samples.

Results

Effective refractory periods

Anterograde AV node effective refractory period. The anterograde AV node effective refractory period was able to be determined by means of the atrial pacing technique in only three patients in the control state and in five after lidocaine. This was because 1:1 accessory pathway conduction usually persisted at the maximum rate of atrial pacing with 1:1 AV conduction. The point of failure of 1:1 AV node conduction therefore could not be readily determined as the His deflection was then obscured in the ventricular depolarization wave of the His bundle electrogram. In three patients therefore the mean anterograde AV node effective refractory period as determined by this technique decreased by 5% after lidocaine from 495 ± 116 msec to

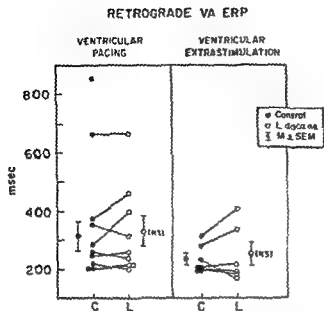


Fig 2 Retrograde VA effective refractory period (ERP) as determined by the ventricular pacing and extrastimulus techniques

472 ± 110 msec without statistical significance ($p = 0.5$) (Fig 1)

The anterograde AV node effective refractory period was able to be determined by means of the atrial extrastimulus technique in 10 patients in the control state and after lidocaine. In two patients with increasing prematurity of atrial extrastimuli in the control state accessory pathway conduction persisted to the point of failure of AV conduction. In these cases the point of failure of AV node conduction could not be readily determined as the His deflection was obscured. In these 10 patients therefore the mean anterograde AV node effective refractory period as determined by this technique decreased by 1% after lidocaine from 258 ± 26 msec to 256 ± 20 msec without statistical significance ($p = 0.9$) (Fig 1)

Anterograde accessory pathway effective refractory period The anterograde accessory pathway effective refractory period was able to be determined by means of the atrial pacing technique in 11 patients in the control state and after lidocaine. In one patient with intermittent WPW syndrome delta wave not present at the time of the study. In these 11 patients the mean anterograde accessory pathway effective refractory period as determined by this technique increased by 7% after lidocaine from 334 ± 51 msec to

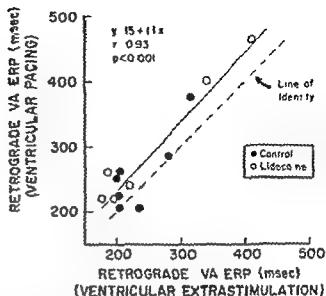


Fig 3 Linear relationship close to the line of identity between the retrograde VA effective refractory period (ERP) as determined by the ventricular pacing and extrastimulus techniques

359 ± 63 msec without statistical significance ($p = 0.2$) (Fig 1)

In these 11 patients the mean anterograde accessory pathway effective refractory period as determined by the atrial extrastimulus technique increased by 1% after lidocaine from 302 ± 28 msec to 303 ± 29 msec without statistical significance ($p = 0.8$) (Fig 1)

Retrograde VA effective refractory period The retrograde VA effective refractory period was able to be determined by means of the ventricular pacing technique in 10 patients in the control state and nine after lidocaine. One to one VA conduction was absent at all rates of ventricular pacing in one patient in the control state and in two after lidocaine so that the exact value of the VA effective refractory period could not be determined in these instances. The technique was not performed in another patient. In nine patients therefore the mean retrograde by 6% after lidocaine from 314 ± 49 msec to 332 ± 51 msec without statistical significance ($p = 0.3$) (Fig 2)

The retrograde VA effective refractory period was able to be determined by means of the ventricular extrastimulus technique in seven patients in the control state and in six of these patients after lidocaine. It was not performed in the three instances of absent 1:1 VA conduction or in two other instances. In six patients there

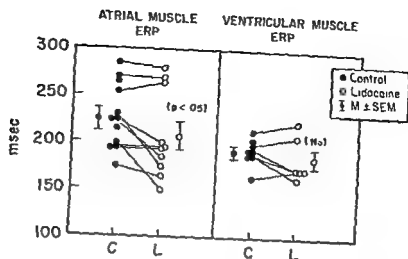


Fig 4 Atrial and ventricular muscle effective refractory periods (ERP) as determined by the extrastimulus technique

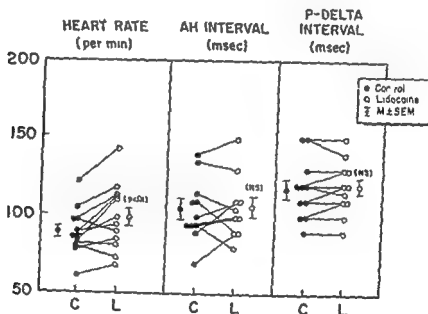


Fig 5 Heart rate and anterograde AV conduction times (AH and P delta intervals) during sinus rhythm

fore the mean VA effective refractory period as determined by this technique increased by 6% after lidocaine from 240 ± 19 msec to 254 ± 40 msec without statistical significance ($p = 0.6$) (Fig 2).

The retrograde VA effective refractory period was estimated by both the ventricular pacing and extrastimulus techniques in 13 instances in the control state and after lidocaine. There was a significant linear correlation between the two techniques ($r = 0.93$, $p < 0.001$) and the line drawn from the linear regression equation was close to the line of identity (Fig 3).

Atrial and ventricular muscle effective refractory periods. The atrial muscle effective refrac-

ry period was determined by means of the atrial extrastimulus technique in 12 patients in the control state and in 10 after lidocaine. In 11 patients therefore the mean atrial muscle effective refractory period significantly decreased by 8% after lidocaine from 226 ± 11 msec to 208 ± 15 msec ($p = 0.04$) (Fig 4).

The ventricular muscle effective refractory period was determined by means of the ventricular extrastimulus technique in eight patients in the control state and in six after lidocaine. In six patients therefore the mean ventricular muscle effective refractory period decreased by 3% after lidocaine from 193 ± 7 msec to 188 ± 10 msec without statistical significance ($p = 0.5$) (Fig 4).

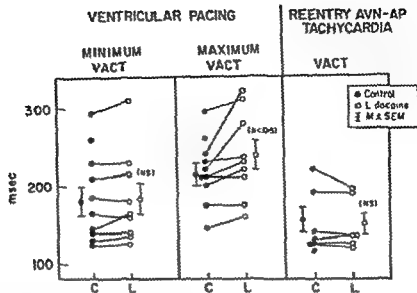


Fig 6 Retrograde VA conduction time (CT) during ventricular pacing (minimum and maximum) and during reentry AV node accessory pathway tachycardia

Conduction times The mean heart rate of the 12 patients significantly increased by 11% after lidocaine from 89 ± 4 /minute to 99 ± 6 /minute ($p = 0.01$) (Fig 5).

Anterograde AV node conduction time The AH interval or the anterograde AV node conduction time was able to be determined during sinus rhythm in 11 patients in the control state and in 10 after lidocaine. In three instances the His deflection was obscured in the delta wave of the His bundle electrogram. In 10 patients therefore the mean anterograde AV node conduction time during sinus rhythm increased by 2% after lidocaine from 105 ± 7 msec without statistical significance ($p = 0.7$) (Fig 5).

Anterograde accessory pathway conduction time The P delta interval an estimate of the anterograde accessory pathway conduction time was able to be determined during sinus rhythm in all patients in the control state and after lidocaine except for the patient in whom delta waves were absent at the time of study. In 11 patients therefore the mean anterograde accessory pathway conduction time during sinus rhythm increased by 2% after lidocaine from 118 ± 6 msec to 120 ± 5 msec without statistical significance ($p = 0.5$) (Fig 5).

Retrograde VA conduction time In nine patients the mean minimum VA conduction time at the slowest rate of ventricular pacing with 1:1 VA conduction increased by 2% after lidocaine from 181 ± 19 msec to 184 ± 20 msec

without statistical significance ($p = 0.2$) (Fig 6). The mean maximum VA conduction time at the maximum rate of ventricular pacing with 1:1 VA conduction significantly increased by 11% after lidocaine from 214 ± 13 msec to 238 ± 19 msec ($p = 0.03$) (Fig 6).

During the studies re entry AV node accessory pathway tachycardia with anterograde AV node and retrograde accessory pathway conduction developed in seven patients in the control state and in six after lidocaine. In six patients therefore the mean retrograde accessory pathway conduction time during re entry AV node accessory pathway tachycardia decreased by 3% after lidocaine from 155 ± 16 msec to 150 ± 14 msec without statistical significance ($p = 0.3$) (Fig 6).

Tachycardia initiation

Incidence and rate of tachycardia Re entry AV node accessory pathway tachycardia was initiated in seven patients in the control state and in six after lidocaine. In six patients therefore the mean rate of the tachycardia increased by 2% after lidocaine from 196 ± 10 /minute to 200 ± 9 /minute without statistical significance ($p = 0.4$) (Fig 7).

Re entry accessory pathway AV node tachycardia with anterograde accessory pathway and retrograde AV node conduction was initiated in one patient in both the control state and after lidocaine. The rate of the tachycardia remained unchanged at 207/minute (Fig 7).

Atrial fibrillation with accessory pathway con

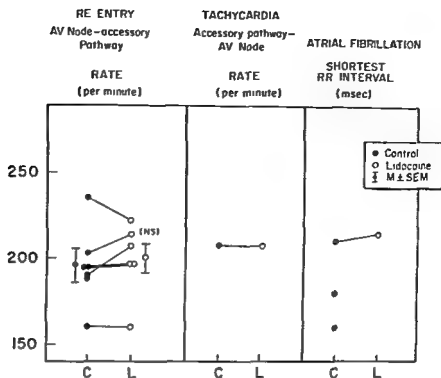


Fig 7 Incidence and rate of tachycardias initiated during the electrophysiologic studies

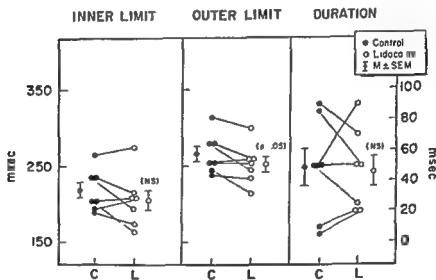


Fig 8 Features of the "tachycardia zone" or the zone of atrial extrastimuli that initiate reentry tachycardia

duction developed in three patients in the control state and in one of these after lidocaine. In the latter patient the shortest RR interval of the ventricular response increased by 2% after lidocaine from 210 msec to 215 msec (Fig 7).

Tachycardia zone: Reentry tachycardia of either type was initiated by atrial extrastimuli in seven patients in the control state and after lidocaine. The tachycardia zone or the zone of coupling intervals of atrial extrastimuli that initiate tachycardia may be described in terms of its

inner and outer limits and its duration. The mean inner limit of the tachycardia zone decreased by 6% after lidocaine from 219 ± 10 msec to 206 ± 13 msec without statistical significance ($p = 0.2$). The mean outer limit significantly decreased by 5% after lidocaine from 267 ± 10 msec to 253 ± 10 msec ($p = 0.02$). The mean duration of the tachycardia zone decreased by 6% after lidocaine from 49 ± 12 msec to 46 ± 10 msec without statistical significance ($p = 0.8$) (Fig 8).

Anterograde accessory pathway AV node of effective refractory period difference. The difference between the anterograde accessory pathway and AV node effective refractory periods has been implicated as a factor in the tendency to develop re entry tachycardia.¹⁰ This relationship is illustrated in Fig 9. It resembles a parabola with an optimal anterograde accessory pathway AV node effective refractory period difference for the initiation of re entry tachycardia by atrial extra stimuli in these patients of approximately 40 msec. When this difference is less than or greater than approximately 40 msec tachycardia initiation by atrial extra stimuli becomes progressively less likely. Where this value could be calculated it was removed from its optimal value by 25 ± 3 msec in the control state (10 patients) and by 26 ± 8 msec after lidocaine (nine patients).

Discussion

In most cases tachycardia in the WPW syndrome occurs on the basis of a re entry circuit formed by the atrial muscle the AV node the His Purkinje system and ventricular muscle and the accessory pathway.¹ Its direction is usually anterograde (across the AV node accessory pathway tachycardia) so that the QRS complexes are normal but occasionally it is reversed (re entry accessory pathway AV node tachycardia) so that the QRS complexes are bizarre consisting of pure delta waves. Occasionally atrial fibrillation and flutter may occur generally with accessory pathway conduction so that the QRS complexes are usually bizarre.¹ Rarely ventricular fibrillation and sudden death may occur being more likely in those patients with paroxysmal atrial fibrillation. Even the former tachycardias however may produce significant hemodynamic impairment requiring urgent therapy. Moreover (1) re entry AV node accessory pathway tachycardia may be conducted with aberrant intraventricular conduction and so may resemble ventricular tachycardia (2) atrial fibrillation with accessory pathway conduction may also resemble ventricular tachycardia if the irregular ventricular response characteristic of atrial fibrillation is not noted and (3) re entry accessory pathway AV node tachycardia and atrial flutter with accessory pathway conduction and a regular ventricular response may be indistinguishable from ventricular tachycardia.

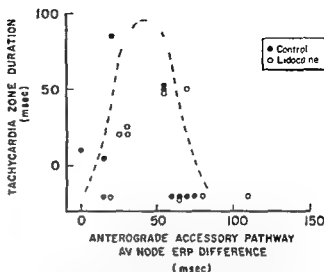


Fig 9 Parabolic relationship between the difference in the anterograde effective refractory periods (ERP) of the accessory pathway and the AV node and the duration of the tachycardia zone. A tachycardia zone duration of 0 means that there was only one coupling interval of atrial extra stimuli that initiated reentry tachycardia. Points below this are in cases where there was no tachycardia initiation by atrial extra stimuli.

Lidocaine is known to be effective in ventricular tachyarrhythmias¹¹ and has been said to be extremely valuable in the WPW syndrome for supraventricular tachyarrhythmias with accessory pathway conduction,¹² suggesting that lidocaine should be administered in either case. Nevertheless as the tachycardias of the WPW syndrome are variable and paroxysmal it is difficult to ascribe to the administration of a drug what may have occurred spontaneously. Because of this and because of possible additional effects of lidocaine this electrophysiologic study was undertaken.

For a drug to be effective intravenously as acute therapy for the tachycardias of the WPW syndrome it should act on part or all of the re entry circuit in one or both directions so as to (a) terminate or decrease the rate of the re entry tachycardias or (b) decrease the rate of the ventricular response in atrial fibrillation and flutter in the case of depression of the accessory pathway or it should act on the atrial or ventricular muscle in such a way as to terminate atrial fibrillation or flutter or ventricular fibrillation.

Anterograde AV conduction. Lidocaine did not significantly increase the mean anterograde effective refractory periods of the AV node or the accessory pathway as determined by atrial pacing or extrastimulation. Accordingly it is not likely to terminate the re entry tachycardias by

this mechanism or decrease the rate of the ventricular response in atrial fibrillation

Rosen and colleagues⁹ reported an increase in the anterograde accessory pathway effective refractory period as determined by atrial pacing in four of six patients and as determined by atrial extrastimulation in one of two patients after the intravenous administration of lidocaine in doses similar to those used in our patients. Some of our patients also developed an increase in the anterograde accessory pathway effective refractory period after lidocaine but a decrease was just as likely and there was no way of predicting a favorable response.

Lidocaine did not significantly increase the mean anterograde conduction time across the AV node or the accessory pathway during sinus rhythm. Accordingly, it is not likely to decrease the rate of the re-entry tachycardia by this mechanism.

Retrograde VA conduction. We have previously found¹ and it is again in evidence in these patients that the atrial pacing technique overestimates the anterograde AV node effective refractory period as compared to the atrial extrastimulus technique but that no such disparity exists in the case of the determination of the anterograde accessory pathway effective refractory period. We attribute the disparity in the former case to the parasympathetic effects of rapid atrial pacing¹ which increase the AV node but not the accessory pathway effective refractory period.² We feel that these considerations also apply in the reverse direction with ventricular pacing. In this study in the determination of the VA effective refractory period there was excellent linear correlation between the techniques of ventricular pacing and extrastimulation and the linear regression equation fell close to the line of identity. This suggests that it was in fact the retrograde accessory pathway effective refractory period that was determined as opposed to the retrograde AV node effective refractory period. Lidocaine did not significantly increase the mean retrograde accessory pathway effective refractory period as determined by ventricular pacing or extrastimulation. Accordingly, it is not likely to terminate re-entry AV node accessory pathway tachycardia by this mechanism.

Ruskin and co-workers¹⁰ reported the effects of intravenous lidocaine 1 mg/kg as a bolus and 4 mg/minute by infusion on retrograde VA con-

duction in patients without the WPW syndrome. As determined by the ventricular extrastimulus technique the mean retrograde His-Purkinje system effective refractory period in four patients significantly decreased by $\geq 13\%$ after lidocaine, from 324 ± 20 msec to 281 ± 31 msec ($p < 0.005$). There were variable effects on the retrograde AV node effective refractory period in 11 patients. Lidocaine would appear unlikely to terminate re-entry accessory pathway AV node tachycardia by this mechanism.

Lidocaine did not significantly increase the minimum retrograde accessory pathway conduction time during ventricular pacing at the slowest rates with 1:1 VA conduction. There was a significant increase in the maximum retrograde accessory pathway conduction time during ventricular pacing at maximum rates with 1:1 VA conduction suggesting that lidocaine may prolong the retrograde accessory pathway conduction time in re-entry AV node accessory pathway tachycardia and so decrease its rate. Nevertheless, such an effect was not manifest in the six patients who developed this tachycardia in the control state and after lidocaine where there was no significant change in the retrograde accessory pathway conduction time.

Atrial and ventricular muscle refractoriness. Lidocaine significantly decreased the mean atrial muscle effective refractory period with no significant change in the mean ventricular muscle effective refractory period. Accordingly, it is not likely to terminate the re-entry tachycardias by this mechanism. A decrease in the atrial muscle effective refractory period may in fact facilitate the development or continuation of atrial fibrillation.

Tachycardia initiation

Incidence and rate of tachycardia. As intravenous lidocaine had minimal or no effect on the effective refractory periods of the components of the re-entry circuit in either direction it was not surprising that re-entry tachycardia was initiated during electrophysiologic study in a similar number of patients in the control state and after lidocaine. Furthermore, as it had minimal or no effect on the conduction time across the components of the re-entry circuit in either direction it was not surprising that there was no significant change in the rates of the tachycardias initiated.

No specific attempt was made to initiate atrial

fibrillation by atrial pacing at very rapid rates. During the course of the routine studies however atrial fibrillation occurred in three patients in the control state and in one of these after lidocaine. In this patient the shortest RR interval of the ventricular response was minimally increased. The shortest RR interval of the ventricular response correlates with the anterograde accessory pathway effective refractory period^{20, 21} and in the two remaining patients the anterograde accessory pathway effective refractory period as determined by the atrial extrastimulus technique decreased by 4% and 20%. Accordingly should atrial fibrillation have occurred after lidocaine in these two patients there would have been no increase and perhaps even a decrease in the shortest RR interval of the ventricular response.

Tachycardia zone The initiation of re-entry tachycardia by atrial extrasystoles may be expected to be less likely when the range of coupling intervals of atrial extrastimuli that initiate re-entry tachycardia is found to be small. Lidocaine did not significantly decrease the duration of this tachycardia zone. If the outer limit of the tachycardia zone is decreased an atrial extrasystole with a coupling interval at this outer limit will no longer initiate re-entry tachycardia. Lidocaine was successful in significantly reducing this tachycardia zone outer limit but only by 5%.

Anterograde accessory pathway AV node effective refractory period difference When the anterograde accessory pathway effective refractory period is relatively great and the anterograde AV node effective refractory period is relatively small there is strong likelihood of an atrial extrasystole finding the accessory pathway refractory and the AV node available for conduction and therefore for the initial event of the re-entry AV node accessory pathway circuit to occur. Completion of this circuit however requires that retrograde accessory pathway conduction be intact and if in any way the retrograde effective refractory period of the accessory pathway parallels the anterograde effective refractory period such conduction will not occur. Theoretically therefore it appears that there is an optimal accessory pathway AV node effective refractory period difference for initiation of re-entry tachycardia by atrial extrasystoles when both the anterograde and retrograde limbs of the re-entry circuit are considered together. Such a relationship has already been reported²¹ and

appeared to be present in our cases. The anterograde accessory pathway AV node effective refractory period difference was as far removed from this optimal value for tachycardia initiation in both the control state and after lidocaine. Thus tachycardia initiation by atrial extrasystoles was just as likely after lidocaine as before.

Clinical implications A number of aspects of the WPW syndrome were not able to be assessed by these studies. These include any possible effects of intravenous lidocaine on the atrial or ventricular muscle in such a way as to prevent the extrasystoles which initiate the other arrhythmias. Any such action however is not of relevance in the assessment of intravenous lidocaine as acute therapy for tachycardia that is already present. Any possible effect of intravenous lidocaine on the atrial or ventricular muscle in such a way as to terminate atrial fibrillation or flutter or ventricular fibrillation likewise was not studied. The significant decrease in the mean atrial muscle effective refractory period however may be expected to maintain rather than terminate atrial fibrillation.

As intravenous lidocaine 1 mg/kg did not significantly depress conduction in either direction in any part of the re-entry circuit studied or alter features related to tachycardia initiation intravenous bolus administration of lidocaine is most unlikely except in isolated unpredictable cases to terminate or decrease the rate of the re-entry tachycardias or to decrease the rate of the ventricular response in atrial fibrillation in patients with WPW syndrome. Nevertheless larger doses than routinely used may produce transient bypass blockade.

Summary

Twelve patients with the Wolff Parkinson White syndrome underwent electrophysiologic study before and after the bolus intravenous administration of lidocaine 1 mg/kg. There was no significant increase in the effective refractory period of the anterograde AV node pathway, the anterograde or retrograde accessory pathway or the atrial or ventricular muscle. Intravenous bolus administration of lidocaine is unlikely to terminate the re-entry tachycardias or decrease the rate of the ventricular response in atrial fibrillation in the WPW syndrome. There was no significant increase in the anterograde or retrograde AV conduction times. Bolus

of lidocaine is unlikely to decrease the rates of the re-entrant tachycardias. In addition, lidocaine failed to alter significantly features related to tachycardia initiation. Except in isolated unpredictable cases, intravenous bolus administration of lidocaine is not likely to be of benefit in the supraventricular tachyarrhythmias of the WPW syndrome.

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Rheumatic mitral stenosis cross-sectional echocardiographic analysis

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Whereas M mode echocardiography proved valuable in recognizing the presence of rheumatic mitral valvular disease^{1,2} its limitations in assessing the severity of the process and predicting the hemodynamic findings are well recognized.³ In contrast cross sectional echocardiography images the mitral valve apparatus from several tomographic views⁴⁻⁶ and allows an assessment of mitral valve orifice size. The use of the short axis view has been applied extensively to estimate the mitral valve orifice size with excellent correlation with hemodynamic data.⁷⁻¹¹ More recently the technical difficulties in imaging the actual mitral orifice using this view have been recognized.¹²⁻¹⁴ The longitudinal left ventricular cross sectional echocardiographic view has been primarily used to recognize rheumatic mitral valvular involvement. However its role in predicting the segmental anatomy and the severity of stenosis has not been fully explored. The purpose of this study was to assess the specific role of the longitudinal left ventricular view in predicting the severity of rheumatic mitral stenosis and to define the spectrum of rheumatic stenosis of the mitral valvular apparatus.

Materials and methods

The control population of 22 normal individuals (mean age 51 ± 10 years, 55% female) identi-

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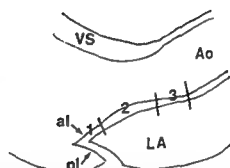


Fig 1 A schematic of the left ventricular longitudinal cross-sectional echocardiographic view demonstrating the ventricular septum (VS), aorta (Ao), left atrium (LA), and the anterior (al) and posterior (pl) mitral valve leaflets. The anterior leaflet was divided into its tip (1), body (2), and base (3).

fied by catheterization were selected to determine the normal mitral valve morphology and leaflet motion. Twenty-one patients with rheumatic mitral stenosis with no or with mild mitral regurgitation and having both hemodynamic and cross sectional echocardiographic studies within a four week period constituted the study population. Their mean age was 61 ± 12 years with 76% females.

Cross sectional echocardiographic views were obtained by the methods outlined by Kisslo and associates¹ and by Silverman and co-workers.¹⁵

All cross sectional echocardiographic studies were obtained using a wide angle 84 degree commercially available phased array system (Varian V 3000) with a transducer containing 32 mounted piezoelectric crystals with a diameter of 1.3×1.2 inches at the skin level. All studies were recorded on video tape (Sanyo) and were later reviewed in real time slow motion and frame by frame analysis. Individual frame selection for figures were

photographed using a Polaroid camera. The quality of these still frame images was significantly graded since only one half of the line density was present during the still framing. *M* mode echocardiographic studies were obtained using a Smith Kline Echoline 20A with a 2.25 MHz transducer. Left ventricular longitudinal and short axis views of the mitral valve were obtained using the conventional approach.¹ The left ventricular longitudinal view was considered adequate when both mitral leaflets were visualized and the continuity of the anterior mitral leaflet with posterior aortic root and the interventricular septum with anterior aortic root were preserved. The anterior mitral leaflet was analyzed in all 22 control individuals to define the normal range of mitral valvular motion in diastole. Subsequently, the mobility of the anterior mitral leaflet in diastole in the study group could be analyzed. The anterior mitral leaflet was arbitrarily divided into three portions: tip body and base. The tip was defined as the leading edge of the anterior mitral leaflet. The base of the leaflet was considered that portion of the leaflet near and at its attachment to the annulus. The body of the leaflet was defined as that part between the tip and the base (Fig 1). The short axis view involved multiple tomographic sections starting at the level of the aortic valve and progressing downwards to the level of the mitral valve and then to the papillary muscles and apex. The short axis view of the mitral valve orifice size was considered adequate only when the multiple tomographic views could be identified in succession and the mitral orifice size could be confidently assessed at the tip of the valve rather than a skewed view off of the true orifice (Fig 2). Gain settings were carefully adjusted as previously recommended. The apical four chamber view was considered adequate when the atrioventricular valves and all four chambers were well visualized.

All cross sectional echocardiographic studies were analyzed by two independent observers.

The mobility of the anterior mitral leaflet was considered normal (as in controls) when the leaflet moved freely and its tip approximated the interventricular septum during diastole. In the study group the tip of the leaflet demonstrated restricted motion due to commissural fusion producing a convex appearance towards the interventricular septum during diastole. This doming

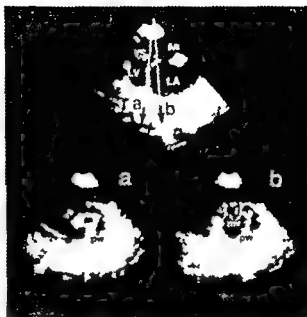


Fig 2 The top cross-sectional echocardiogram reveals a left ventricular longitudinal view demonstrating the ventricular septum (*h*), left ventricular cavity (*LV*), aorta (*AO*) and left atrium (*LA*). The two superimposed white lines (*a*, *b*) show the planes in which the short axis views labeled *a* and *b*^{*} (below) were derived. The short axis view labeled *a*^{*} depicts the mitral valve orifice at the mitral valve tip whereas, the short axis view labeled *b*^{*} depicts the apparent mitral valve (*me*) orifice size when the echocardiographic beam was skewed off of the mitral valve tip. View *a*^{*} represents the actual mitral valve orifice area in this patient with mitral stenosis whereas a normal mitral valve orifice area would have been predicted if the estimation was made using view *b*^{*} which was obtained off of the tip of the mitral valve. *pu* = posterior left ventricular wall.

effect was estimated as severe (Fig 3A) if the convexity of the leaflet was striking and collided with the interventricular septum in diastole and was considered mild to moderate (Fig 3B) if the convexity of the anterior leaflet did not approximate the septum.

End systolic frames were analyzed for the presence of mitral valve prolapse pattern namely: a leaflet position beyond the mitral ring toward the left atrium at end systole.

Severity of mitral stenosis was defined using hemodynamic findings. Mitral valve orifice size was measured using Gorlin's formula.¹ Severe mitral stenosis was considered present when valve orifice size was less than 1 cm, moderate between 1 and 1.5 cm, and mild when more than 1.5 cm. Left ventriculography was performed in the right anterior oblique view and the mitral valve was analyzed for any systolic prolapse in this view using the criteria of Cohen and associates.¹

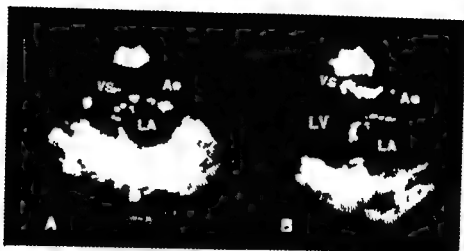


Fig 3 The left ventricular longitudinal cross sectional echocardiographic view in panel A represents severe doming of the anterior mitral valve leaflet (small white arrow). The ventricular septum (VS), aorta (Ao) and left atrium (LA) are also shown. Panel B demonstrates mild to moderate anterior mitral valve leaflet doming.

Table 1 Correlation of the pattern of anterior mitral leaflet motion and severity of mitral stenosis

| Pattern of anterior mitral leaflet motion by cross sectional longitudinal view | | Severity based on catheterization findings | | |
|--|---------------------------------|--|----------|--------|
| | | Mild | Moderate | Severe |
| Pattern A (N = 8) | Mild/moderate doming (N = 2) | 1 | 1 | 0 |
| | Severe doming (N = 6) | 2 | 2 | 2 |
| Pattern B (N = 8) | | 0 | 1 | 7 |
| Pattern C (N = 1) | | 0 | 0 | 1 |

Results

I Patterns of anterior mitral leaflet motion in diastole. The anterior mitral leaflet could be adequately analyzed in all 21 patients with mitral stenosis. Three patterns of leaflet motion were identified (Table I and Fig 4).

Pattern A Restricted motion of the leaflet's tip with doming of the whole leaflet was seen in eight patients. Mild to moderate doming was noted in two of eight and severe doming was noted in six of eight. Hemodynamic data identifying severe mitral stenosis were noted in only two of eight patients, all of whom had severe diastolic doming of the anterior leaflet.

Pattern B Restricted motion of the leaflet's tip and body with mild doming of the basal portion of the leaflet was seen in eight patients. Fig 4

demonstrates this pattern, showing that the base of the leaflet is moving during the cardiac cycle while the tip and body have restricted motion. Hemodynamically severe mitral stenosis was present in seven of these eight patients.

Pattern C Restricted motion of the entire leaflet was seen in 5 patients, all of whom had hemodynamically severe mitral stenosis. Fig 4 shows an example of this pattern of severely restricted leaflet motion during systole and diastole.

Thus the pattern of echocardiographic longitudinal view of the anterior leaflet motion correlated well with the hemodynamic severity of the mitral stenosis. However, a close correlation was not always observed in Pattern A (Fig 5).

II Extent of thickening of the anterior mitral leaflet. Table II details the extent of thickening of the anterior mitral leaflet and the correlation with the degree of hemodynamic severity. Five patients had no thickening of the anterior mitral leaflet, while three showed thickening involving primarily the tip, ten involving the tip and body, and three involving the entire leaflet. Patients with valvular thickening were on the average a decade older than those without thickening (Table II). The extent of thickening correlated with the severity of mitral stenosis (Table II). Thus the spread of thickening of the mitral anterior leaflet appeared to extend from tip and body towards the base. When the leaflet was not thickened or only thickened at its tip, the frequency of severe mitral stenosis was less than if the leaflet's body or the entire leaflet was thickened.



Fig 4 These three left ventricular longitudinal cross-sectional echocardiographic views were obtained from three different patients with mitral stenosis, and show the observed patterns of anterior mitral valve leaflet motion. Panel A demonstrates doming of the anterior mitral valve leaflet (white arrow) with leaflet thickening isolated to the tip. Panel B shows thickening primarily of the tip and body with relative sparing of the base of the mitral valve leaflet (single white arrow). Panel C demonstrates little anterior mitral valve leaflet motion with severe thickening of the tip, body, and base. Ao = aorta; LV = left ventricle; LA = left atrium; and VS = ventricular septum.

III Patterns of anterior mitral leaflet in systole Mitral valve prolapse pattern was noted in three of eight patients with Pattern A leaflet motion. All three patients showed severe doming of the anterior mitral leaflet (Fig 6) and two of these three had hemodynamic evidence of severe mitral stenosis. The posterior mitral leaflet was not prolapsed in any of these three patients nor did left ventriculography reveal prolapse in any patient. Mitral valve prolapsing motion can be seen with rheumatic mitral stenosis (Fig 6) but appears to require a pliable anterior leaflet with severe commissural fusion and doming. The presence of mitral valve prolapse pattern by cross-sectional echocardiography suggested hemodynamically severe mitral stenosis. The lack of posterior leaflet prolapse (Fig 6) suggested that the anterior leaflet prolapse is unrelated to the floppy valve syndrome but probably was a systolic rebound phenomenon of the markedly domed leaflet motion in diastole.

Discussion

The limitations of M mode echocardiography in assessing the severity of mitral stenosis are recognized. The recent introduction of cross-sectional echocardiography has enhanced the ability to estimate the severity of the rheumatic process and can actually image the true orifice size of the mitral valve. Henry and associates were the first to document an excellent correlation between the mitral valve area as estimated

Table II Extent of thickening of the anterior mitral leaflet in mitral stenosis

| Number of patients | Mean age (yr ± SD) | Site of thickening | | | Catheterization proven severe MS |
|--------------------|--------------------|--------------------|------|------|----------------------------------|
| | | Tip | Body | Base | |
| 5 | 57 ± 15 | — | — | — | 1/5 |
| 3 | 66 ± 15 | — | — | — | 1/3 |
| 10 | 63 ± 10 | + | + | — | 9/10 |
| 3 | 63 ± 3 | + | + | + | 3/3 |

Symbol: — = no thickening; + = thickening; MS = mitral; M = none

by hemodynamic data and short axis cross-sectional echocardiographic imaging of the mitral orifice size. However, the following potential limitations to this technique are: varying orifice size due to different gain settings; cross-sectional short axis view of the mitral valve skewed from the true orifice; inability to assess subvalvular contribution due to valvular obstruction; and lack of standardization of the measurement of the orifice area.

The value of the longitudinal view obtained by cross-sectional echocardiography has not been fully explored as a means to assess the severity of mitral stenosis. Since the entire length of the mitral leaflet is visualized by this view, different features of leaflet motion and thickening may reflect different hemodynamic alterations. In this study, we have attempted to define the spectrum of cross-sectional echocardiographic findings of



Fig 5 A comparison of the left ventricular longitudinal views from two patients (top panels) with the short axis tomographic views (bottom panels) are shown. Patient A demonstrated severe doming of the anterior mitral valve leaflet comparable to the degree of doming seen in patient B (upper right hand panel). The short axis view of the mitral valve orifice in each of these patients taken at the tip of the mitral valve revealed that although patients A and B had similar degree of doming of the anterior mitral valve leaflet on the longitudinal view, their mitral valve orifice areas were substantially different. Patient A had a 1.1 cm² and patient B had a 2.4 cm² mitral valve orifice area (LA = ventricular septum, LV = posterior left ventricular wall, LA = left atrium, LV = left ventricle).

the rheumatic mitral annular involvement using the view.

The anterior mitral leaflet motion pattern as measured by the longitudinal cross sectional echocardiographic view is useful in estimating the functional extent of mitral stenosis. When mitral stenosis is present there was loss of the normal motion of the tip of the anterior mitral leaflet. The motion of the leaflet was still pliable during diastole, showing a normal motion of the leaflet against the interventricular septum. The degree of doming was dependent on two factors: the pliability of the mitral anterior leaflet and the extent of commissural fusion. Thus with mitral fusion there was less leaflet doming and the hemodynamic severity of the stenosis was less. In contrast, anterior mitral leaflet motion showing severe doming correlated more closely with severe

stenosis especially when the leaflet abutted against the interventricular septum. Severe anterior leaflet doming by the longitudinal view does not always predict however the severity of mitral stenosis (Fig 5).

When the extent of thickening of the anterior mitral leaflet was analyzed it was evident that thickening tended to occur in older patients that the tip of the leaflet was the site of the earliest thickening and that the thickening tended to spread from tip towards the base. Heavily thickened leaflets with basilar involvement tended to have mitral annular calcification. The extent of thickening of the anterior mitral leaflet predicted the severity of mitral stenosis especially when the entire leaflet was thickened and no doming motion was seen.

The occurrence of mitral valve prolapse in the presence of mitral stenosis has been previously observed.²¹ Nichol and colleagues found that 60% of their patients with mitral stenosis did show a systolic prolapsing pattern of the anterior mitral leaflet. Others²² have found that mitral valve prolapse in mitral stenosis was uncommon and that the presence of both entities was merely the coexistence of two separate disease entities. Our study is in support of the findings of Nichol and associates as we encountered systolic mitral leaflet prolapse in 30% of our patients with Pattern A which was correlated with the severity of leaflet doming and the degree of stenosis. This suggested that the prolapse motion as seen in patients with a pliable anterior mitral leaflet occurs when the tip is restricted in motion due to commissural fusion and the body prolapses in systole as a rebound phenomenon of the markedly domed leaflet in diastole. The lack of posterior mitral leaflet prolapse in these patients by echocardiography and left ventriculography suggested further that this prolapsing pattern is unrelated to the floppy valve syndrome.

In conclusion the anterior mitral leaflet motion pattern on longitudinal cross sectional echocardiography may help predict the hemodynamic severity of mitral stenosis. The thickening of the mitral leaflet in rheumatic disease appears to spread from leaflet tip to base and appears to involve the annulus only when the entire leaflet is thickened. Mitral valve prolapse appears in patients with rheumatic mitral stenosis when the anterior leaflet is pliable and severely domed and is probably a rebound phenomenon in systole of the diastolic domed leaflet.



Fig 6 Diastolic (Diast.) and systolic (Syst.) left ventricular longitudinal cross sectional echocardiographic views are presented from a single patient with mitral stenosis. The diastolic view demonstrates severe doming of the anterior mitral valve leaflet (large white arrow) which in systole becomes mitral valve prolapse (small white arrow) as a rebound phenomenon. The posterior mitral valve leaflet is not prolapsed. AO = aorta LA = left atrium LV = ventricular septum

Summary

Twenty one patients with rheumatic mitral stenosis diagnosed by both M mode echocardiography and hemodynamic findings were subjected to detailed cross sectional echocardiographic studies. The age of the patients ranged from 27 to 79 years with 76% females. Left ventricular longitudinal short axis and apical four chamber cross sectional echocardiographic views were obtained in each patient. Three predominant patterns of anterior mitral leaflet motion on left ventricular longitudinal view were observed and correlated with the severity of mitral stenosis. Pattern A (eight patients) with diastolic leaflet doming and restricted leaflet tip motion. Pattern B (eight patients) with restricted tip and body leaflet motion and Pattern C (five patients) with the entire leaflet motion restricted. Mitral valve prolapse as a rebound phenomenon was observed in three patients who had marked leaflet doming in Pattern A and two had severe obstruction. The longitudinal cross sectional echocardiography was superior to the apical view in assessing the diastolic doming motion of the anterior mitral leaflet. Thus longitudinal cross sectional echocardiographic analysis of the pliability and degree of doming of the anterior mitral leaflet is valuable in estimating the severity of mitral stenosis.

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Pathology of the heart in acromegaly: anatomic findings in 27 autopsied patients

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As a disease entity, acromegaly was first described by Marie in 1886.¹ Cardiac enlargement and congestive heart failure were added to the symptom complex of acromegaly by Huchard in 1895 and by Fournier in 1896. Although cardiomegaly is a common finding in acromegaly, its pathogenesis remains obscure after numerous studies and much scrutiny by various investigators in the last 50 years. The proposed etiologic factors of cardiac enlargement in acromegaly include hypertension, coronary artery disease, valvular heart disease, compensatory hypertrophy, secondary to increased work load induced by generalized splanchnomegaly and somatomegaly, and direct humoral effects of the growth hormone. A specific entity of heart muscle disease in acromegaly (acromegalic cardiomyopathy) has also been suggested by some investigators.

Postmortem findings of the heart in acromegaly are surprisingly scarce since the autopsy information was available in only a fraction of patients in most published large series of cases. In this report we review the cardiac pathology of 27 autopsy cases of acromegaly seen in a single institution over a 60 year period and compare our morphologic findings with those described in the literature.

Patients and methods

We reviewed a total of 41 autopsy cases of acromegaly culled from the Mayo Clinic autopsy

records of 1919 to 1978 but only 27 cases with adequate clinical data and complete postmortem examination were included in this study, comprising 16 males and 11 females. The mean age of the 27 patients at death was 50 years (range = 13 to 83 years). All but four patients died before 1960. The diagnosis of acromegaly was almost exclusively clinical because radioimmunoassay of plasma growth hormone is a relatively recent procedure.

All 27 patients had the characteristic acromegalic appearance including broad hands, feet, and digits which had increased in size with progression of the disease and often required larger gloves, shoes, and rings. Prominent jaw, coarse facial features, visual disturbances (especially bitemporal hemianopia), and persistent headache were also common clinical findings.

The gross specimens and histologic sections of the hearts of all 27 patients were available for review. Significant coronary atherosclerosis was defined as one or more vessels with 75% or greater cross-sectional area luminal narrowing. Significant aortic atherosclerosis was defined as the abdominal aorta showing 50% or greater surface area involvement by atherosclerosis. The patients' organ weights were compared with the expected weights of organs according to the body weight or the body height. Expressing the expected organ weight as 100%, the patients' organ weights were calculated as a percentage of the expected weights by the formula: $\text{Actual Weight/Expected Weight} \times 100\%$. All existing and newly cut additional histologic sections of the hearts were evaluated with no prior knowledge of the heart size or the patient's clinical data. Histological diagnosis of myocardial hypertrophy was made independently of whether or not the heart weight was above the expected weight.

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Table 1 Summary of major clinical and pathologic findings in 27 cases of acromegaly

| Case | Sex and age (yr) at death | HT | Clinical heart disease ² | Body wt and body length | Actual organ wt and percent of normal wt in parenthesis | | | | CAD | Aortic disease | Myocardial disease ³ | Cause of death |
|---|---------------------------|----|-------------------------------------|-------------------------|---|-----------------|-----------------|------------------|-----|----------------|---------------------------------|--------------------------|
| | | | | | Liver | Spleen | Kidneys | Heart | | | | |
| Group I (11 patients with less than 10 year history of acromegaly) | | | | | | | | | | | | |
| 1 | F 36 | — | — | 50 kg 161 cm | 1830 g (125%) | 260 g (217%) | 330 g (115%) | 260 g (100%) | — | — | MH IF | Post-op hypophysectomy |
| 2 | F 51 | — | — | 52 kg 157 cm | 1510 g (106%) | 135 g (113%) | 350 g (122%) | 275 g (107%) | — | — | MH IF CI | Post-op hypophysectomy |
| 3 | F 22 | — | — | 62 kg 163 cm | 2315 g (161%) | 570 g (475%) | 455 g (158%) | 190 g (71%) | — | — | — | Post-op hypophysectomy |
| 4 | F 33 | + | — | 68 kg 173 cm | 2190 g (150%) | 287 g (235%) | 345 g (120%) | 340 g (119%) | — | — | MH IF SVD | Post-op hypophysectomy |
| 5 | M 13 | + | — | 111 kg 184 cm | 3015 g (166%) | 275 g (145%) | 490 g (158%) | 345 g (99%) | — | — | MH CI | Post-op hypophysectomy |
| 6 | F 34 | — | — | 85 kg 166 cm | 1810 g (124%) | 201 g (168%) | 384 g (133%) | 400 g (146%) | — | — | MH IF MC | Post-op hypophysectomy |
| 7 | M 46 | + | MR MS CHF | 102 kg 190 cm | 4000 g (220%) | 365 g (202%) | 636 g (207%) | 379 g (106%) | — | — | MH IF SVD | Carcinoma of stomach |
| 8 | F 41 | — | — | 80 kg 170 cm | 1540 g (107%) | 150 g (125%) | 235 g (82%) | 310 g (97%) | — | — | MH IF | Post-op hypophysectomy |
| 9 | F 69 | — | AR CHF | 77 kg 173 cm | 1325 g (96%) | 152 g (138%) | 270 g (94%) | 410 g (143%) | — | — | MH IF | Post-op hypophysectomy |
| 10 | F 30 | — | — | 68 kg 176 cm | 2492 g (177%) | 193 g (161%) | 503 g (170%) | 371 g (110%) | — | — | MH IF CI | Post-op hypophysectomy |
| 11 | M 44 | — | — | 114 kg 170 cm | 2000 g (109%) | 225 g (155%) | 535 g (171%) | 600 g (187%) | — | — | MH CI | Post-op thyroidectomy |
| Group II (16 patients with more than 10 year history of acromegaly) | | | | | | | | | | | | |
| 12 | M 51 | — | AR AS CHF | 76 kg 180 cm | 2095 g (114%) | 200 g (138%) | 360 g (111%) | 1300 g (370%) | — | + | MH IF MC | Congestive heart failure |
| 13 | M 73 | + | AF CHF | 60 kg 169 cm | 2075 g (150%) | 140 g (100%) | 415 g (133%) | 550 g (172%) | — | + | MH IF SVD | Carcinoma of lung |
| 14 | F 67 | + | Old MI | 52 kg 162 cm | 1350 g (98%) | 120 g (109%) | 280 g (97%) | 400 g (152%) | — | — | MH IF MC | Stroke |
| 15 | M 57 | + | Old MI CHF | 86 kg 172 cm | 2870 g (191%) | 310 g (214%) | 555 g (177%) | 775 g (238%) | + | + | MH IF CI SVD | Congestive heart failure |
| 16 | M 3 | + | AP CHF Old MI | 80 kg 171 cm | 2000 g (145%) | 400 g (276%) | 355 g (120%) | 725 g (224%) | + | + | MH IF MC | Congestive heart failure |
| 17 | M 64 | — | — | 108 kg 200 cm | 3040 g (175%) | 790 g (545%) | — | 480 g (127%) | — | — | MH IF CI | Pyelonephritis, uremia |
| 18 | M 67 | — | Old MI | 7 kg 172 cm | 2110 g (121%) | 180 g (121%) | 540 g (173%) | 490 g (102%) | — | — | MH IF CI | Glioblastoma |
| 19 | M 30 | — | — | 64 kg 170 cm | 2250 g (123%) | 400 g (255%) | 470 g (152%) | 450 g (118%) | — | — | MH IF MC SVD | Hydrocephalus |
| 20 | M 36 | — | — | 91 kg 170 cm | 2203 g (123%) | 533 g (344%) | 513 g (164%) | 485 g (147%) | — | — | — | Post-op hypophysectomy |
| 21 | F 63 | + | AR CHF | 100 kg 170 cm | 2104 g (152%) | 510 g (464%) | 570 g (198%) | 575 g (198%) | — | — | MH IF CI | Post-op thyroidectomy |

HT = hypertension defined as blood pressure recordings $\geq 160/90$ mm Hg

AF = atrial fibrillation AR = aortic regurgitation AS = aortic stenosis CHF = congestive heart failure MI = myocardial infarction MR = mitral regurgitation MS = mitral stenosis

*CAD = significant coronary artery disease defined as one or more intramural coronary arteries with $\geq 75\%$ cross-sectional luminal narrowing

Abdominal aorta with $\geq 4\%$ surface area involvement by atherosclerosis

CI = cellular lymphomatous infiltration of heart muscle IF = interstitial fibrosis MC = myocarditis MH = myocardial hypertrophy SVD = small vessel disease of intramural branches of coronary arteries

Table 1 cont d

| Case | Sex and age (yr) at death | HT | Clinical heart disease ^a | Body wt and body length | Actual organ wt and percent of normal wt in parentheses | | | | CAD | Aortic disease | Myocardial disease ^b | Cause of death |
|-----------------|---------------------------|----|-------------------------------------|-------------------------|---|-----------------|-----------------|-----------------|-----|----------------|---------------------------------|--------------------------------|
| | | | | | Liver | Spleen | Kidneys | Heart | | | | |
| Group II cont'd | | | | | | | | | | | | |
| 22 | M 44 | + | CHF | 100 kg 168 cm | 2892 g (137%) | 230 g (119%) | 410 g (131%) | 653 g (218%) | - | - | MH IF | Post-op hypophysectomy |
| 23 | M 47 | - | CHF | 86 kg 160 cm | 3100 g (168%) | 125 g (66%) | 45 g (159%) | 525 g (165%) | - | - | MH IF | Post-op thv reductomy |
| 24 | M 81 | + | - | 96 kg 191 cm | 1960 g (142%) | 230 g (159%) | 390 g (125%) | 550 g (149%) | + | + | MH IF SVH | Pulmonary embolism |
| 25 | F 83 | + | MR MS | 48 kg 158 cm | 1335 g (113%) | 135 g (123%) | 280 g (97%) | 400 g (219%) | - | + | MH IF MC | Stroke |
| 26 | M 50 | + | CHF | 73 kg 172 cm | 2583 g (140%) | 316 g (187%) | 473 g (151%) | 473 g (146%) | - | - | MH IF MC | Post-op vocal cord polypectomy |
| 27 | M 40 | - | - | 73 kg 166 cm | 1967 g (109%) | 19 g (136%) | 300 g (96%) | 310 g (97%) | - | - | MH IF CI | Pulmonary embolism |

Results

We assigned the 27 autopsy cases arbitrarily into two groups according to the duration of the disease. Group I comprised 11 patients who died within 10 years of clinical onset of acromegaly. Group II comprised 16 patients who died 10 or more years after the onset of acromegaly. The major clinical and pathologic findings are summarized in Table I.

Cause of death. Of the group I patients nine had hypophysectomy and one had thyroidectomy; all of these 10 patients died in the first postoperative week from surgical complications. The remaining and the sole nonsurgical group I patient died of carcinoma of the stomach. Only two of the 11 (18.2%) group I patients had organic heart disease clinically: one had mitral valve disease and congestive heart failure (Case no. 7) and the other had aortic regurgitation and congestive heart failure (Case no. 9). The cause of death of group II patients was more varied (Table I): five from surgical complications (two hypophysectomy, two thyroidectomy, and one vocal cord polypectomy); three from cardiac failure; two from stroke; two from pulmonary emboli; one each from pyelonephritis, hydrocephalus, glioblastoma, and carcinoma of the lung. Although cardiac failure was the cause of death of only three of the 16 group II patients, seven other patients (a total of 10 or 37% of the total series of 27) had clinical evidence of congestive heart failure (Table I).

Organ weights. Compared with the expected organ weights according to the individual's body

weight and body height, the vast majority of both group I and group II patients had splanchnomegaly, including increased heart size: hepatomegaly 93%, splenomegaly 93%, renomegaly 81%, and cardiomegaly 81%. Only nine patients (33%) in the entire series had heart weights exceeding 500 g, all but one in group II (Table I). The largest heart in the series, 1300 g, was 3.7 times the expected weight (Fig. 1). The increase in heart size appeared to be related to the duration of the disease (Fig. 2) and unrelated to the presence of hypertension or coronary artery disease. The proportions of patients with heart weights greater than the expected weights in group I and group II were 63.6% (seven of 11) and 93.8% (15 of 16) respectively. The difference was statistically significant ($p < 0.01$) according to the rank-sum test. Cardiomegaly was disproportionate to hepatomegaly, splenomegaly, and renomegaly in 33%, 26%, and 30% respectively (Figs. 3, 4, and 5). None of the hearts showed asymmetric septal hypertrophy.

Cardiac abnormalities. Clinical hypertension, defined as blood pressure recordings of 160/95 mm Hg or higher, was present in three (27%) of group I and nine (56%) of group II patients (Table I). Eleven of the 12 (91%) hypertensive patients had cardiomegaly. However, cardiomegaly was also common among the nonhypertensive acromegaly patients, being present in 73% (11 of 15) of cases. Four of the group I and none of the group II patients were diabetic. Significant coronary artery disease was present in three of 27 cases.



Fig 1 A normal sized 350 g heart (on the left) is dwarfed by the giant 1300 g acromegalic heart (on the right)

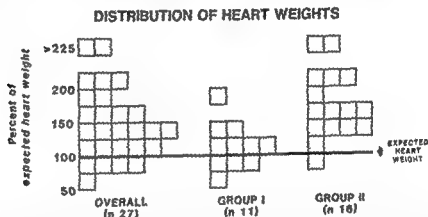


Fig 2 Histograms showing distribution of heart weight in acromegalic patients. Expected heart weight according to patient's body weight and body length is expressed as 100 percent. Group I patients died within 10 years of onset of acromegaly, and group II patients died 10 or more years after the onset of acromegaly.

(11) the ages of these three patients were 57, 73 and 83 years. Gross evidence of old myocardial infarction was found in four of 27 cases (15%). Again each of these four patients was 57 years old or older. Significant atherosclerosis of the abdominal aorta was found in six of 27 cases (22%); five of these six patients were 75 years old or older. Aortic and mitral valvular heart disease was present in eight of 27 cases (29%); two had aortic regurgitation, two had mitral stenosis and regurgitation (one a histologically or morphologically rheumatic aetiology in origin) and one had calcific aortic stenosis and regurgitation secondary to old bacterial endocarditis.

Review of myocardial histopathology generally showed varying degrees of myocardial hypertrophy and interstitial fibrosis (Fig 6). Myocardial

hypertrophy was present to some extent in 23 (85%) of 27 cases and involved the myocardium of both ventricles. Focal myocardial fiber disarray (Fig 7) was observed in five cases (19%). Interstitial fibrosis was seen in 23 (85%) of 27 cases almost invariably accompanying myocardial hypertrophy. Other histologic findings which appeared frequently were interstitial lymphomononuclear infiltrate and small vessel disease. The myocardium in 16 of 27 cases (59%) showed a continuum of changes from mild nonspecific interstitial cellular infiltration to true myocarditis. Myocarditis which may be focal or diffuse (Fig 8) was observed in seven hearts (26%). Six of 27 patients (22%) had significant wall thickening of the small intramural branches of the coronary arteries unrelated to myocardial scar tissue (Fig 9). Four

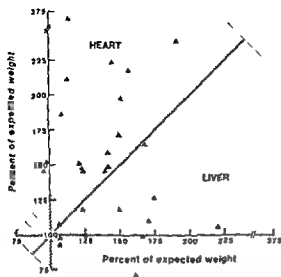


Fig 3 Comparison of the corresponding actual heart weight (ordinate) and actual liver weight (abscissa) in acromegalic patients. Expected organ weight according to patient's body weight and body height is expressed as 100 percent. The shaded area represents $\pm 25\%$ of the expected (100%) organ weights. Points outside the shaded area are regarded as disproportionate organomegaly: heart to the left, liver to the right of the diagonal solid line.

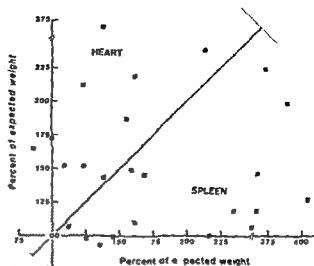


Fig 4 Comparison of the corresponding actual heart weight (ordinate) and actual spleen weight (abscissa) in acromegalic patients. Expected organ weight according to patient's body weight and body height is expressed as 100 percent. The shaded area represents $\pm 25\%$ of the expected (100%) organ weights. Points outside the shaded area are regarded as disproportionate organomegaly: heart to the left, spleen to the right of the diagonal solid line.

of the six patients who had small vessel disease of the heart were clinically hypertensive and one of the four also had diabetes mellitus. The prevalence of the various pathologic changes of the heart in group I and group II patients are compared in Table II.

An additional autopsy finding that occurred commonly was thyroid enlargement. Only five of the 23 thyroids examined at autopsy were normal; the remaining 18 (78%) were adenomatous (15 cases) or showed Hashimoto thyroiditis (three cases). It was noted that four of the 27 patients in this series had undergone thyroidectomy for hyperthyroidism.

Discussion

Cardiac failure as a major cause of morbidity and mortality in acromegaly has been repeatedly emphasized in the past.

However, most of the previously published studies of cardiovascular disorders in acromegaly are either purely clinically oriented or have included only a small number of autopsied patients. There are also reports of large series that do not deal with cardiac findings in any detail. The results of a recent prospective study of 57 patients by McGuffin and associates¹⁷ are at variance with many of the

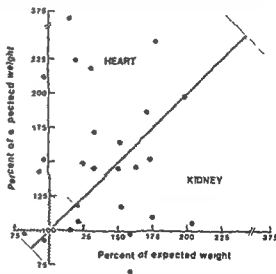


Fig 5 Comparison of the corresponding actual heart weight (ordinate) and actual kidney weight (abscissa) in acromegalic patients. Expected organ weight according to patient's body weight and body height is expressed as 100 percent. The shaded area represents $\pm 25\%$ of the expected (100%) organ weights. Points outside the shaded area are regarded as disproportionate organomegaly: heart to the left, kidneys to the right of the diagonal solid line.

conclusions of the earlier studies, notably the lack of correlation between hypertension, cardiac disease, and the growth hormone concentration in acromegaly. Unfortunately, only eight autopsied

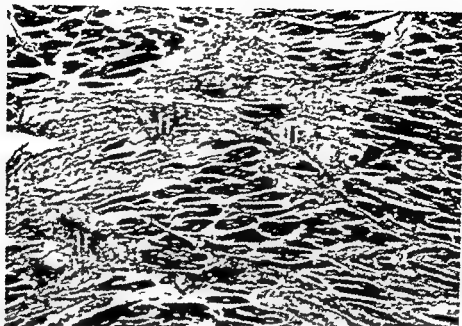


Fig 6 Typical histologic appearance of acromegalic heart showing interstitial fibrosis (IF) and hypertrophied myocardial fibers (Mallory Heidenhain stain; original magnification $\times 100$)

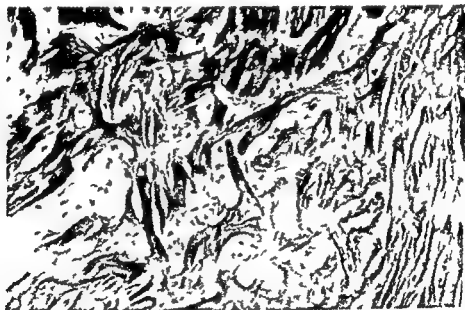


Fig 7 Presence of focal myocardial fiber disarray in acromegalic heart (Hematoxylin-eosin; original magnification $\times 100$)

cases were reported in the report by McGuffin and colleagues.¹¹

Autopsy Series of Acromegaly Acromegaly is sufficiently uncommon that the number of autopsy cases from a single institution is necessarily limited. In our survey of case records of acromegaly from five different medical centers, Wright and coworkers¹² were able to identify a total of 194 cases of which there were 22 deaths

but the postmortem reports were available for only 26 patients. The 27 patients included in our series were selected (on the basis of availability of tissue specimens for review) from a total of 40 autopsy cases in the Mayo autopsy record from 1919 to 78. In this 60-year period, the total number of autopsies performed at Mayo was 4,767, representing an autopsy incidence of acromegaly of 1 in 1,116.

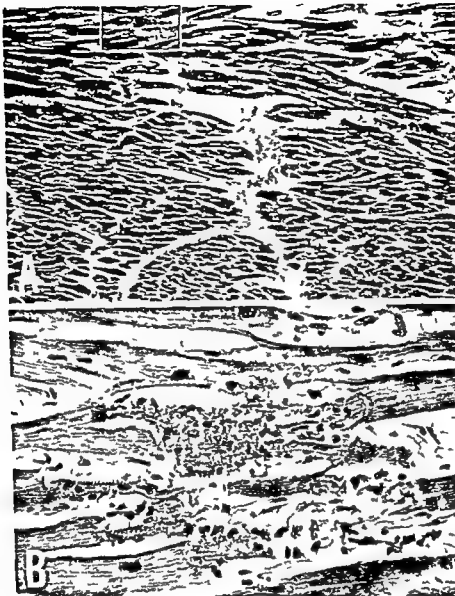


Fig 8 A Histologic appearance of myocarditis in acromegalic heart B The boxed area in A is seen at higher magnification showing individual myocyte necrosis and lymphomononuclear cell infiltrate (Hematoxylin-eosin A original magnification $\times 48$ B original magnification $\times 300$)

Review of our autopsy cases of acromegaly bears many disadvantages that are inherent to all retrospective studies but the potential benefits of understanding the pathogenesis of a disease process with the aid of detailed postmortem findings should be equally obvious. Because all but four deaths in our series occurred before 1960 we lack data to comment on the significance of growth hormone concentration in relation to cardiovascular disorders of acromegaly. This aspect has been fully discussed by McGuffin and associates. The separation of our 27 autopsy cases

into two groups though arbitrary (based on the known duration of acromegaly from diagnosis to death) makes interesting comparison with reference to the mortality cause of death and cardiac abnormalities (Table II).

Mortality and cause of death. Patients with acromegaly are known to have a reduced life expectancy. In the collective series of 194 cases reviewed by Wright and colleagues¹⁴ 26% of deaths occurred before the age of 50 years and 64% by the age of 60 years. Even higher figures were noted in an earlier study of 100 cases by

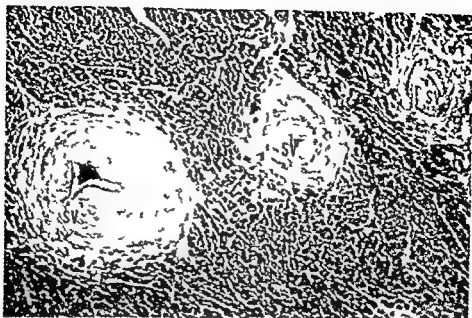


Fig 9 Histologic appearance of proliferative wall thickening of small intramural vessel (SV) in acromegalic heart (Hematoxylin-eosin, original magnification $\times 499$)

Table II Cardiac pathology in acromegaly (autopsy series)

| Group | Group I (n = 11) | Group II (n = 16) | Total (n = 27) |
|-------------------------------------|------------------|-------------------|----------------|
| Sex ratio (M/F) | 3/8 | 13/3 | 16/11 |
| Mean age (yr) at death | 39.5 | 57.9 | 50 |
| Hypertension ($\geq 160/90$ mm Hg) | 3 (27%) | 9 (56%) | 12 (44%) |
| Diabetes mellitus | 4 (36%) | 0 | 4 (15%) |
| Clinical heart failure | 2 (18%) | 8 (50%) | 10 (37%) |
| Cardiomegaly | 7 (64%) | 15 (94%) | 22 (81%) |
| mean heart weight (g) | 349 | 618 | 446 |
| Coronary artery disease | 0 | 3 (19%) | 3 (11%) |
| Aortic atherosclerosis | 0 | 6 (38%) | 6 (22%) |
| Valvular heart disease | 2 (18%) | 3 (19%) | 5 (19%) |
| Myocardial hypertrophy | 10 (91%) | 15 (94%) | 25 (93%) |
| Interstitial fibrosis | 8 (73%) | 15 (94%) | 23 (85%) |
| Cell infiltrate or myocarditis | 5 (45%) | 11 (69%) | 16 (59%) |
| Small vessel disease | 2 (18%) | 4 (25%) | 6 (22%) |

Group I patients died within 10 years of diagnosis of acromegaly. Group II patients died more than 10 years after diagnosis of acromegaly. H indicates expected weight by body weight or body length only as compared to 10% of normal. Cardiac megaly was recognized clinically in 10 patients with ≥ 7.5 cm. Aortic atherosclerosis was recognized in 6 patients with $\geq 50\%$ surface area in athero-lesion. Cell infiltrate or myocarditis was recognized in 16 patients with histological myocardial hypertrophy within the normal range (no cardiomegaly).

Evans and co-workers¹⁰ who reported 50% of deaths before the age of 30 years and 89% by the age of 60 years. There was a heavy bias of surgical deaths in our group I patients: nine of the 11 patients died before 1940 in the pre-antibiotic era, also at the time of the more hazardous transfrontal craniotomy for resection of pituitary tumors. All seven (20% of the series) cardiovascular deaths (three cardiac failure, two stroke and

two pulmonary embolism) occurred in group I patients in whom acromegaly was diagnosed before 30 years. A greater prevalence of cardiovascular disorders among patients who had their acromegaly longer was also noted in the prospective series reported by McGuffin and associates.¹¹

As has already been noted by Wright and colleagues,¹² the particular specialty of the hospital

tal may in part determine the observed causes of death in acromegaly. Of the two older studies diabetic coma was the most common cause of death in a report published in 1927⁴ and intra cranial extension of the pituitary tumor was the commonest cause of death in another report published in 1964.¹⁰ In the survey conducted by Wright and co workers¹² increased mortality was found to be associated with hypertension and clinical diabetes but not with chemical diabetes. The 26% incidence of deaths from cardiovascular disorders in our series was in close agreement with the 24% reported by Wright and colleagues.¹²

Pathogenesis of cardiomegaly. Organomegaly including cardiac enlargement has been so consistently identified with acromegaly that Levene and Miller²⁰ considered it worthwhile to report a case because the heart was normal in size. Although the literature is replete with reports of acromegalic hearts in excess of 1000 grams^{4,5,7,8} it is still more common to find acromegalic hearts weighing several hundred grams less than the kilogram range. The mean heart weight was 486 grams in our series of 27 patients but a trend toward progressive cardiac enlargement with longer duration of acromegaly was evident. The mean heart weight of our group I patients (acromegaly less than 10 years) was 348 grams whereas the mean heart weight of our group II patients (acromegaly more than 10 years) is 618 grams. Of the 22 patients in whom cardiomegaly was found at autopsy, only seven (36%) were recognized to have roentgenologic evidence of cardiac enlargement clinically.

Disproportionate cardiomegaly (cardiac enlargement proportionately greater than enlargement of other visceral organs) has often been cited¹⁰ as a uniform finding in acromegaly. This notion was unsupported by our autopsy data when cardiomegaly was compared with the enlargement of the liver, spleen and kidneys in the same patient (Figs 3, 4 and 5).

Premature or accelerated atherosclerosis as a cause for the cardiac hypertrophy in acromegaly was first suggested by Huchard in 1895⁴ and an increased incidence of significant coronary and aortic atherosclerosis in acromegalic patients has been repeatedly cited since then.^{4,10,12} This was not substantiated by autopsy data since only 11% of cases had significant coronary artery disease and 22% of cases had significant aortic

atherosclerosis (Table II). All signs were found in patients at an age when more advanced atherosclerosis would be expected normally.

Valvular heart disease in association with acromegaly was seldom discussed in the past. Courville and Mason³ cited no data but stated that cardiac disease in patients with acromegaly was probably due to some etiologic factors other than valvular disease. Indeed valvular disease was not uncommon (19%) in our patients and appeared to contribute little to cardiac hypertrophy in acromegaly.

The importance of hypertension in cardiomegaly is highly contentious. Reports of the incidence of high blood pressure in acromegaly range from 8 to 57%.^{11,12,14} The overall incidence of hypertension was 44% in our series; it occurred twice as commonly in group II as in group I patients (Table II). Some authors postulate an important causal relationship between hypertension and cardiac enlargement in acromegaly,^{9,11} but others disagree.^{1,12} Although five of the seven largest hearts in our series were found in hypertensive subjects, 11 (73%) of the 15 nonhypertensive patients also had cardiomegaly (Table I). Typically the hypertension was mild, uncomplicated and responsive to drugs as previously noted by McGuffin and co workers.¹

Similarly it seemed unlikely that diabetes was a major etiologic factor of cardiomegaly in acromegaly; only four (15%) of our 27 autopsied patients were diabetic. In reviewing Harvey Cushing's patients Coggeshall and Root⁴ found 26 (17%) diabetes in 153 cases of acromegaly. The average interval between the onset of acromegaly and diabetes was 9.2 years. According to the authors the clinical character of the diabetes associated with acromegaly did not show any greater variation in severity, resistance to insulin and life expectancy than was seen in a large group of diabetic subjects without acromegaly.

The direct effects of growth hormone on heart size remains an unsettled issue. DeGrandpre and Raab¹ showed that repeated doses of growth hormone in the presence of a normal work load caused cardiac hypertrophy in rats. Some authors feel this also applies to human hearts while other investigators deny it.^{11,12} According to McGuffin and colleagues,⁹ hypertension was the only abnormality that correlated with the plasma growth hormone concentration but a marked

reduction in plasma growth hormone concentration although not usually normal, did not influence the hypertension

Some authors^{15,17} have suggested the possibility of a specific entity *acromegalic cardiomyopathy*, in which cardiomegaly is present in the absence of hypertension, atherosclerosis, or severe valvular disease. Indeed, 33% (nine of 27) of cases in our series fell within this category (Table I). This possibility merits further consideration though the currently available evidence does not fully support it. Two recently reported clinical studies¹⁸ have shown that most acromegalic hearts function normally even when their mass is considerably enlarged and subclinical cardiac dysfunction is uncommon among asymptomatic patients with acromegaly. However, in an earlier study Jonas and co-workers¹⁹ reported a high incidence of subclinical cardiac muscle disease in 10 acromegalic patients on the basis of abnormal systolic time intervals.

Another possibility that pituitary products other than growth hormone may be responsible for the unexplained cardiomegaly in acromegaly also warrants serious consideration. Curtarelli and Ferrari²¹ have recently reported an interesting case of massive cardiomegaly with heart failure in a 42-year-old hyperprolactinemic woman in whom a pituitary tumor had been treated by radiotherapy five years previously. Since prolactin is known to exert metabolic growth hormone-like effects in animals and in man, the authors conjecture that prolactin hypersecretion might induce or maintain cardiac disease in patients with pituitary tumors. In a preliminary survey of 35 hyperprolactinemic subjects Curtarelli and Ferrari²¹ have found five with raised blood pressure and four two of whom were normotensive with cardiomegaly on chest roentgenographs.

Histopathology of acromegalic hearts. The occurrence of myocardial hypertrophy and interstitial fibrosis in acromegalic hearts is well known.² The heart weight of three patients with myocardial hypertrophy were within the normal range. Nonspecific lymphomononuclear cell infiltration (nine of 27 cases or 33%) true myocarditis (seven of 27 cases or 26%) and small vessel disease (six of 27 cases or 22%) have rarely been recognized or described previously. Small vessel disease and foci of mild cellular infiltrates

in the interstitium have been seen occasionally in hypertrophied hearts from a variety of causes, including acromegaly, but their etiology is unclear. Nor is the etiology of myocarditis in acromegaly known. Morphologically, the myocarditis in acromegaly is reminiscent of myocardial lesions observed in experimental animals after norepinephrine infusion^{22,23} and in patients with pheochromocytoma.²⁴ It is speculated that the myocarditis in acromegaly might be causally related to the altered homeostasis of endogenous catecholamine secretion. Of interest, a recent report by Van Loon²⁵ has shown abnormal plasma catecholamine responses to the suppressive effects of bromocriptin (a dopaminergic agonist) and luteinizing hormone-releasing hormone in acromegalics. Whatever the mechanism might be in the development of myocardial lesions in acromegalics, myocarditis is a possible contributing factor to cardiac failure in these patients though not necessarily the cause of cardiomegaly.

Conclusions. Cardiomegaly was common but not inevitable, in acromegaly, being present in 81% of our series of 27 autopsy cases. The enlarged heart seldom exceeded 200% (i.e., twice) of the expected heart weight according to the patient's body weight and body height. Contrary to the prevailing view, disproportionate cardiomegaly (in comparison with hepatomegaly, splenomegaly, and renomegaly) was not a uniform finding; it occurred in one-fourth to one-third of our cases. Cardiomegaly appeared to be related to the duration of acromegaly, and was present in both hypertensive and nonhypertensive subjects. Our data did not support another common belief that premature or accelerated atherosclerosis and diabetes were causally related to acromegaly and cardiac failure in acromegaly. The possibility that a specific acromegalic cardiomyopathy may exist cannot be discounted by the currently available evidence. The significance of small vessel disease and myocarditis in acromegaly has not been discussed in earlier pathologic studies of acromegaly and warrants further probing.

Summary

The morphologic characteristics of cardiac enlargement in poorly understood partly because of detailed anatomic studies

pathogen remain paucity as per

out elsewhere rheumatic fever has a truly wide spectrum of presentation and based on our observations a condition called mild rheumatic fever may indeed exist. In our series we found that about one-fourth of the patients with rheumatic heart disease had presented with one or several episodes of recurring and migrating polyarthralgia with associated low grade fever one week to several months before carditis was diagnosed. It would thus seem that perhaps in areas of high incidence some patients develop mild attacks of rheumatic fever which are unrecognized and subsequently develop a recurrent attack which is often looked upon as the first attack. And the reason for failure to diagnose the mild attack is a simple and absolute reliance on the Jones criteria.

It is perhaps advisable that until further knowledge is gained regarding the possibility of such sequences of events particularly in areas of high incidence the clinician should watch for patients with arthralgia, high ASO titer and elevated erythrocyte sedimentation rate. Such instances would certainly deserve closer observation regarding future streptococcal throat infection and occasionally in the presence of strong family or sibling history of rheumatic fever one may justify prophylaxis for some time. Most certainly the parents of such children deserve a thorough orientation with regard to rheumatic fever. Due to the rarity and non specificity of subcutaneous nodules and erythema marginatum their usefulness in the diagnosis of rheumatic fever can be questioned. Thus, in the future a modified approach to the long honored Jones criteria may be warranted.

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Reply

To The Editor

We wish to thank Dr Aryanpur who comes to America from the rheumatic fever front line of a (ever so painfully!) developing country for his flattering and thoughtful comments. The possibility that malnutrition early in life predisposes to rheumatic fever is intriguing especially since experimental studies have shown that chronic moderate protein deficiency increases susceptibility to group A streptococcal infections in mice as one of us and El Sadr noted in an earlier review more slanted toward pathogenesis. Dr Aryanpur's advice that the clinician watch for patients with arthralgia, high ASO and elevated ESR is well taken and so is the option of prescribing prophylaxis in some cases that do not quite fulfill the Jones criteria with pedantic completeness. After all the Jones criteria are a guide to the clinician not a clinician. And who can draw the line between a mild arthritis and a severe arthralgia with any certainty? As Daniel McCarty is fond of saying (only half in jest) an arthralgia is often an arthritis minus a good physical examination.

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Beta blockers and running

To the Editor

In a letter to the JOURNAL, Doctor Adrian Williams relates his experience of jogging while being on therapy with 80 mg propranolol daily for mild hypertension (AM HEART J 98 542 1979). He states that before a marathon "I allow myself the luxury of stopping my treatment... this seems the equivalent of a 20 pound weight loss and my performance improves by at least 20 to 30 seconds per mile."

The experience of Doctor Williams is probably shared by a number of physically active men on beta blockers and it seems important to clarify to what extent such therapy affects the physical capacity. We have recently completed a study

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VOLUME 100

JULY DECEMBER 1980

(Int J Sports Med in press) where the effects of 80 mg propranolol and 100 mg atenolol and placebo (double blind design) on the 2 000 m running time was measured in a group of healthy volunteers and related these results to muscle fiber composition. As expected individuals with a high percentage of slow twitch fibers ran faster both times than those with a high percentage of fast twitch fibers. However when on propranolol the performance was relatively more impaired in individuals with a high percentage of slow twitch fibers than in those with a high percentage of fast twitch fibers. Individuals with a high percentage of slow twitch fibers took 20% to 30% longer to complete their 2 000 m running. On atenolol 100 mg the same individuals needed less than 10% longer to complete the 2 000 m running. Thus cardioselectivity (β selectivity) seems to be of importance to joggers.

Hypertensive individuals previously accustomed to physical activity can expect a certain degree of deterioration of their performance capacity when treated with beta blockers. It seems important that adequate information about these side effects of beta blockers is included in the over all information to hypertensive patients.

However it also seems important to warn against unguided withdrawal of antihypertensive drug therapy.

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Reply

To the Editor

It is interesting to have the data of Dr Kayser and his colleagues to support my anecdotal experience with beta blockers and exercise. The 20% to 30% slowing they noted in the 2 000 m time of individuals with a high percentage of slow twitch fibers (presumably those best equipped for running long distances) correlates well with this. I am of course intrigued to think that cardioselective blockade might impede my training less but then the value of such "loaded" training would then be reduced.

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Lo—the poor Eskimos!

To the Editor

Dr Oster's Editorial in the November 1980 issue of the *Journal of the American Heart Association* (Vol 1, No 11, April 1980) is a welcome contribution to the discussion of the relationship between diet and heart disease. In his editorial Dr Oster states that a diet high in saturated fat and cholesterol is an

important factor for a high incidence of coronary heart disease. Dr Oster argues that to establish a causal relationship it must be shown that all population groups with a high saturated fat and cholesterol intake also exhibit a high incidence of atherosclerosis. This is decidedly not the case with the French, the Eskimos, and the Masai, all populations consuming diets high in saturated fats.

The Eskimos are probably the most frequently quoted, or rather—as factual research in contrast to popular assumption has shown—misquoted example used to establish the controversy. Most researchers found that Eskimo groups living a relatively traditional life style consumed despite their predominantly carnivore diet not more but substantially less fat than other North Americans. Furthermore the fats they consumed although derived from animals were not highly saturated as presumed by Oster and others. In fact, a much higher content of long chain polyunsaturated fatty acids than prevailing in North American diets was found in diets of Greenland, Alaskan, and Canadian Eskimos. Platelet lipid analysis in Greenland Eskimos reflected their high consumption of omega 3 polyunsaturated fatty acids, and this resulted in a significantly longer bleeding time due to a reduction in platelet aggregation.

These recent biochemical and physiological findings may explain earlier epidemiological observations that Eskimos were relatively free of thrombotic cardiovascular diseases but suffered from increased bleeding tendencies with undue frequency of severe postpartum hemorrhage and Rheeb's syndrome. The degree of deviation from modern North American norms or the inversely related thrombotic and bleeding tendencies in various Eskimo population groups shows clear trends in geographical distribution and changes with time best explained by changes in their diet.

Eskimos do therefore provide a good example for and against the validity of the fourth report of the American Heart Association Committee on Nutrition and similar recommendations issued in recent years in various countries.

I hope that drawing attention to these facts will help to relieve the Eskimos from being used as false witnesses for the fat lobby, a practice entrenched by repetition of popular myths never supported by factual research. Indeed, the example provides valid ammunition for the side against dietary intervention. I suspect that the other two population groups used in your editorial argument against the recommendations of the Nutrition Committee—namely the Masai and the French—are also not very suitable examples. The Masai are subjected to frequent periods of famine and regularly have to walk long distances as nomadic cattle herders. Most French men drink fair amounts of wine. Famine, physical exertion, and wine drinking all tend to elevate high density lipoproteins which may counteract the effect of low and very low density lipids and cholesterol. There may be other complicating factors evident to observers more familiar with local conditions in France and East Africa than I am.

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Reply

To the Editor

It would indeed be presumptuous of me to enter into an argument with Dr Schaefer about the diet of the Eskimos. I respect his expertise on this subject. However in its imbalance the Eskimo diet does not approximate the American Heart Association Committee on Nutrition's suggested dietary proportions nor do the Eskimos have high serum cholesterol values. Eskimo summer food was found to consist of 3 protein 21% fats and 46% carbohydrates. With this high protein consumption it is understandable how the name "Eskimo" or eater of flesh" was derived. Eskimos prefer to be called Inuit (man).

The low heart attack rate of the Eskimos ascribed to their intake of eicosapentaenoic acid (EPA) which might be partially substituted for arachidonic acid thereby reducing thrombogenesis. However the diet which causes bleeding tendencies in the flesh-eating Inuit seems to have no influence on serum cholesterol. I do not think Dr Schaefer would suggest such an unbalanced diet for the North American population at large.

It is disconcerting to me that Dr Schaefer falls into the

common trap of shunning commonly known findings in order to prop up the faltering diet heart cholesterol hypothesis. I have studied the nutrition of the Masai and published my findings. Their diet includes 60% saturated fats from curdled milk. It is ludicrous to equate their lack of coronary heart disease with the walking of long distances and frequent periods of famine. The lumber workers of East Finland, an agrarian population expend much more of their caloric energy in pursuing their livelihood than do nomadic cattle herders. They live in a lower stress situation than an urban population and still have the highest coronary heart disease rate in the world. I hope that Dr Schaefer is not serious when he accepts the wine drinking habits of French men as the reason for their experiencing less coronary heart disease than similar American men with the identical risk factor constellation despite the documented high saturated fat intake of the French. This naïveté of western findings contrary to one's favorite idea is shared by a blemish who blames the differences in coronary heart disease incidence between European and American men on the European food deprivation of World War II, another alibi. Even the mentors of the Framingham Study have changed their opinion about serum cholesterol. "The previous position that virtually all of the lipid information pertaining to coronary heart disease resided in the serum total cholesterol must be (accordingly) modified."

Self-styled and chest-thumping experts transpose a paucity of nutritional knowledge into an abundance of diverse and questionable advice on altering nutrition and the food supply system of the nation. A brouhaha was created in May 1969 by the recommendation on fats and cholesterol in the diet by the Food and Nutrition Board of the National Academy of Sciences, National Research Council. The Board's action was consistent with its recommendations of 1970. However slanted nutrition research in the political arena has fostered dissemination and varied and unsubstantiated recommendations. Examples are: (1) U.S. Senate Select Committee on Nutrition and Human Needs, *Dietary Goals for the United States*; (2) U.S. Department of Agriculture and the U.S. Department of Health, Education and Welfare, *Nutrition and Your Health: Dietary Guidelines for Americans*; and (3) the Surgeon General's report on health promotion and disease prevention, *Healthy People*. Each differs in its stance on cholesterol and fats, and all are out on a limb. Proponents of dietary changes have not come to a meeting of the mind and stay in different directions, thereby confusing the American consumer. The dissonance of recommendations in the ranks of the AHA's Committee on Nutrition, which was the theme of my Editorial, has spread and is now to be found in most nutrition scenarios of politically inspired organizations.

Quis pecunia eius ducta? (Who's money his diet?)

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Author index*

A

- ARON H L (See Lutz et al) 349
 ARAMS HERBERT L (See Salvy et al) 323
 ARONG MICHAEL R Infectious hazards of mouth to mouth resuscitation 339 (Annot)
 ARACHI MARI (See Hamed et al) 463
 ARMS DOUGLAS F (See Salvy et al) 323
 ARNET A J Effective coronary care and mortality rates, 403 (Letter to Editor)
 ARNAD SAIED Verapamil therapy 211 (Letter to Editor)
 ARAM MORIS AND GOLDSTEIN STEVEN Echocardiographic features of a stenotic porcine aortic valve 517
 AS LUIS E (See Moreyra and Alday) 134
 AS MAHID FAYEMI A OLUSEGUN MALCOLM DANIEL AND BRAUN EVELYNNE V Intraventricular thrombosis in polycythemia vera: A cause of intractable cardiac failure 370
 ASPOUR MASSOUD TARBATI CYAVOUSH AND NAZARIAN IRAJ Right ventricular endomyocardial fibrosis: A simulating ECG 859
 ASPERN HARVEY L (See Viden et al) 590
 ALPERT JOSEPH III (See Haffajee Alpert and Dalen) 1013
 ALPERT JOSE A (See Suarez et al) 618
 ASBROSSE JOHN A MARTINEZ EULOGIO E, MELLER JOSE GORLIN RICHARD RICHARD AUGUSTO D HERRMAN MICHAEL V AND TEICHHOLZ LOUIS F Hemodynamic correlates of late diastolic motion of the aortic root 433
 ASHBY DAVID W (See Su et al) 332
 ANDERSON RAY G Idiopathic mitral valve prolapse: A sudden death 941 (Letter to Editor)
 ANGELO PIER FEDERICO (See Paolillo et al) 763
 ANZELLEVITCH C (See Jalife and Anzilevitch) 178
 ARAI TORU (See Hamed et al) 465
 ARMENIAN HAROUTUNE K (See Sawaya Mujum and Arminian) 144
 ARNMAN ARISTER (See Ryden et al) 1007
 ARORA RAMESH (See Paul, Arora and Rani) 673
 ARAMPAL KASHANI IRAJ On rheumatic fever in children 847 (Letter to Editor)
 AVISSAR R (See Berliner et al) 134

B

- BAIN W H (See Taylor Bain and Morton) 933
 BALLANTYNE D (See Bastian et al) 1017
 BAIN FRITS W (See Wellens et al) 934
 BAI ON ODED (See Sutton and Bar Or) 778
 BARNETT PETER A LAKS MICHAEL M MANDEL WILLIAM J AND YAMAGUCHI IWAO The electrophysiological effects of intravenous idocaine in the Wolff Parkinson White syndrome 23
 BARTECCCHI CARL E Cardiopulmonary resuscitation—an element of sophistication in the 18th century 580 (Annot)
 BASS JOHN L SHRIVASTAVA SAVITRI GRABOWSKI GREGORY A DESNICK ROBERT J AND MOLLER JAMES H The M mode echocardiogram in Fabry's disease 807
 BASSAN MAYER M Branham's sign with atrial fibrillation 411 (Letter to Editor)
 BASTA LOFTY L Reply 768 (Letter to Editor)
 BASTIAN B C MACFARLANE P W McLAUCHLAN J H BALLANTYNE D CLARK R HILLIS W S RAE A P AND HUTTON I A prospective randomized trial of tocamide in patients following myocardial infarction 1017
 BALKMAN JERRY L CURTIS ROBERT A AND COVINSKY JOEL O Effects of antiarrhythmics in ischemic models 947 (Letter to Editor)
 BEDAZOVSKY BERT (See Shoenfeld et al) 179
 BENIS CHARLES E (See Hakki et al) 441
 BENNETT III H (See Ramsdale and Bennett) 931

- BERCHLIS BERT (See Branje and Berghuis) 409
 BERLINER DEAN H SHOENFELD Y AVISSAR R AND PINHAS J Central retinal vein thrombosis in a patient with primary pulmonary hypertension 134 (Letter to Editor)
 BYTOCCHI SANDRO (See Vigorito et al) 782
 BETHRI AMAD O TLBAU JULIO SANZ GINES MAGRICA JORGE AND NAVARRO LOPEZ FRANCISCO Relief of angina by pericardial muscle resection of myocardial bridges 223
 BEWISER I TER D (See How Strachan and Bewsher) 4
 BIAMING FL H J SCHLAG W AND SCHROEDER II J Isotopic pattern of motion of the aortic root correlate of left atrial volume changes
 BIGGER I W J AND WELD FRANCIS M Shortcoming with Lown grading system for observational clinical studies in ischemic heart disease
 BISSETT JOE T (See de Souza et al) 631
 BLACK MARTIN M (See Marmor and Black) 9
 BLACK THOMAS M (See Markov et al) 639
 BLUM MATHIAS DAVID S (See Vlay et al) 907
 BOYAN JAMES R (See Brennan and Bonn) 201
 BONZANI GIULIO (See Vigorito et al) 782
 BOICEN ROBERT J (See Romanelli et al) 617
 BOVE ALFRED A (See Santamore et al) 857
 BOWEN THOMAS F (See Chun et al) 940
 BRAAT SIMON J (See Wellens et al) 934
 BRANJE JOHN PH A AND BERCHLIS BERT Adsorption of NTC 409 (Letter to Editor)
 BRAUN EVELYNNE V (See As et al) 520
 BRANNAN F JAMES AND BOYAN JAMES R Effects of ouabain on the electrophysiological properties of subendocardial Purkinje fibers surviving in regions of acute myocardial infarction 201
 BRIDGES WALLACE (See Leatham and Bridges) 947
 BUELL JAMES C AND ELIOT ROBERT S Psychosocial and behavioral influences in the pathogenesis of acquired cardiovascular disease 723
 BUCHI WILLIAM J KRALIOS ALEXANDROS C TSAGARIS THEOPHILLOS J AND KUIDA HIROSHI Effect of arterial pressure on left ventricular O₂ consumption coronary blood flow and reserve capacity following coronary occlusion 617
 BULKLEY BERNARDINE H (See Schuster and Bulkley) 306
 — (See Moore et al) 610
 — (See Vlay et al) 907
 BULCH G E Certain principles in the management of heart disease and pregnancy 775
 — Of cardiac causalgia Horner's syndrome and the cardiac dermatome 938 (Annot)
 — Of 1910 595
 — Of papillary muscle dysfunction murmurs 178 (Annot)
 — Of right ventricular congestive heart failure 267 (Annot)
 — Of saphenous vein arteriosclerosis 931 (Annot)
 — Of senile anemia 401 (Annot)
 — Of the mitral valve and arrhythmias 583 (Annot)
 — Of the Q wave and myocardial infarction 57
 — Of viral nephritis 59 (Annot)
 — Of walling and dyspnea of congestive heart failure 548 (Annot)
 — Reply 591 (Letter to Editor)
 BURCH P R J Smoking and coronary disease 471
 BURCH J E CLIMAN J A G AND DUNCAN W J LA Hypertrophy versus aneurysm 61 (Letter to Editor)
 BURY BARBARA AND JONES DANIEL Of bibliographies and medical librarians 491 (Letter to Editor)

C

- CABIN HENRY S LESTER LUCILLE A AND ROBERTS WILLIAM C Congenital heart disease with tricuspid valve of the echocardiogram in delineating the location of a left to right shunt 563
 CALFFE RICHARD V (See Nathan Mason and Calfee) 1091

atherosclerosis in the Masai in *Myocardiology in Africa* Nairobi Africa 1974 E A Community (CIS) Chap = 1 209

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Rupture of myocardium and mitral valve replacement

To the Editor

In their article in the January 1980 issue of the AMERICAN HEART JOURNAL Cobbs and associates¹ have presented eight cases of rupture of the myocardium as a result of mitral valve replacement involving severance of the chordae tendineae.

We have been measuring the fiberpath angles of the myocardium in humans and other mammals for some years now and have shown conclusively that the angle change transition from epi to endocardium in the normal heart is smooth and predictable. The fiberpaths obey a theorem of Clairaut which states that $r \cos \alpha = \text{a constant}$. This translates into radius times the cosine of the angle tangential to the epicardium is a constant.

The fiberpath angles at epicardium (and at endocardium) are dependent upon the shape and size of the heart and the thickness of the myocardium. If the wall is thick—i.e. the ratio of the inside diameter to the outside diameter (r/r_0) in the contracted state is small the angles are likely to be steeper at epicardium (~ 60 degrees ± 10 degrees) and at endocardium (~ 50 degrees ± 10 degrees) than if the ratio is large (α at epicardium ~ 60 degrees ± 10 degrees at endocardium ~ 40 degrees ± 10 degrees, relative to the longitudinal axis running through the left aortic valve commissure and the apex of the left ventricle). At least, that is what we have found. If the epicardial fiberpaths can be seen and if the wall thickness is known, a very rough estimation of the endocardial fiberpath angles can be made. In fact, if the epicardial angle is known and the r/r_0 ratio is known, the angles can be estimated again very roughly through the whole thickness of the myocardium by drawing a straight curve from say ~ 70 degrees to 50 degrees. If we divide the wall thickness into quantiles, the epicardial quantile is in balance with the endocardial quantile in accordance with the Clairaut theorem. The quantile next inside epicardium is in balance with the quantile next inside endocardium and so on. With this method, experimentally, it is obvious that rupture of the chordae tendineae in mitral valve replacement leads to the myocardium just basal to the papillary muscle rupture, in association with the epicardial fiberpath at that site. The fiberpath is branched because it is a branched structure in the left ventricle adjacent to the predominant fiberpath. It is a thin structure, the stability of its branches. If the structure is not ruptured must

and does occur. Fig. 3 (Case No. 2) of Cobbs and associates' article shows dramatically that an attempt at readjustment was made. It failed. Balance could not be restored. The figure also shows the transition from the midwall cross-cut fibers on the right, via those cut at intermediate oblique angles, to those which the authors call "plunge fibers" that we suspect are fiberpaths that had attempted to restore Clairaut balance but failed.

Leaving the chordae tendineae attached to the posterior leaflet intact preserved the Clairaut balance. Ideally all chordae should be left intact, but if severance is unavoidable, perhaps collagen sutures longitudinally oriented from the free end of the papillary muscle would take up the load longitudinally.

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Reply

To the Editor

I thank Ms Ross and Dr Streeter for their thoughtful letter and regret not having been previously familiar with their detailed anatomical work which offers elegant theoretical ground for expecting the complication we described. As they imply the structure we call the mitral loop is merely part of a complex system of epicardial to endocardial fiberpaths. It is a pleasure to learn that our concept of a dynamic balance of tension between epicardial and endocardial members of the loop may have mathematical validity. We believe that real ventricular disruption has been around for a long time often in latent or only partly expressed form. But the advent of cardioplegia and perhaps, true trauma from the new dynamic theses have set the stage for a fuller realization of the underlying pathology.

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Cyclophosphamide cardiomyopathy

To the Editor

The Annotation on anthracycline cardiotoxicity by Heranson and Frei¹ very nicely summarizes both acute and chronic

- CAMPBELL, RONALD W F Placebo controlled study of prophylaxis of ventricular arrhythmias in acute myocardial infarction 993
- CAPONE ROBERT J (See Grodman Capone and Most) 763
- CARASCA EMILIAN (See Cotoi et al) 763
- CAREY RITA A (See Santamore et al) 852
- CARLINER, NATHAN H., FISHER MICHAEL L. CROUTHAMER WILLIAM G. NARANG PREM K. and PLOTNICK GARY D Relation of ventricular premature beat suppression to serum quinidine concentration determined by a new and specific assay 483
- CARLYLE PETER F (See Zobel et al) 81
- CARR R KEITH (See Roden et al) 15
- CARUZZO CARLO GASCHING GIANNI TRONI WALTER and CREMO ROSSANA Toxic polyneuropathy and toxic hepatitis related to long term perhexiline maleate therapy 270 (Letter to Editor)
- CASELLI GIOVANNI (See Zeppilli et al) 281
- CHANDY K GEORGE JOHN T JACOB and CHERIAN GEORGE Coxsackievirus and chronic valvular heart disease 578 (Annot)
- CHAUDRON J M and LEBACQ E G Romano Ward syndrome treated by left stellectomy and intracavitary stimulation 313 (Annot)
- CHEN CHIN C (See Naito et al) 34
— (See Mardelli et al) 29
- CHEFRIAN GEORGE (See Chandy John and Chertan) 578
- CHIL D (See Cocco et al) 878
- CHUN PATRICK K C RAJFER SOL I DONOHUE DENNIS J BOWEN THOMAS E. and DAVIA JAMES E Reply (Letter to Editor) 940
- CLARK R (See Bastian et al) 1017
- COBBS B WOODFIN JR Reply 946 (Letter to Editor)
- COCCO G STROZZI C CHU D. and PANSINI R Torsades de pointes as a manifestation of mexiletine toxicity 478
- COHEN LAWRENCE S (See Langou et al) 458
- COHEN SIDNEY (See Long and Cohen) 567
- COHEN JAY M (See Zobel et al) 81
- COKKINOS DENNIS V. TARTALIS GEORGE D. HEIMONAS FLIAS T. and GARDIKAS CONSTANTINE D Comparison of the inotropic action of digitalis and isoproterenol in younger and older individuals 87
- COMPATRIAL (MARRIS JOHN F VINCE HUGH S SACKS BARRY MCARDLE COLIN and RAMIRIZ ALBERTO Echocardiographic diagnosis of left ventricular thrombi 523
- CONDOMELLI MARIO (See Vignato et al) 782
- CONRADSON THOR BJORN (See Radén et al) 1006
- CORRAY ELIOT (See Watt et al) 871
- COTRANIMION IONUT ALFANDRU GEORGEACU CONSTANTIN and CARASCA EMILIAN Pacing below the ventricular rate in terminating ventricular tachycardia and flutter 763 (Letter to Editor)
- COUMPLI THILIP and FIDELL JEFF AMiodarone in the treatment of sinus arrhythmias in children. One hundred thirty five cases 101
- COVINSKY J. P. and HAUMAN (Curtis and Covinsky) 947 (Letter to Editor)
- COX ROBERT H (See Santamore et al) 852
- CRANE ERNEST (See Hada et al) 871
- CREMO ROSSANA (See Caruzzo et al) 270
- CROUTHAMER WILLIAM (See Carliner et al) 483
- CROWE RAYMOND (See Venkatraman et al) 307
- CULHAM J A C (See Burns Culham and Duncan) 177
- CUTLER ROBERT A (See Burns Culham and Duncan) 177

- DEMOULIN J CL (See Waleffe et al) 884
- DESILVA REGIN A, GRABOYS THOMAS B. PODRID PHILIP J. and LOAN BERNARD Cardioversion and defibrillation 881
- DEVENICA ROBERT J (See Bass et al) 801
- DE SOYSA NEEL, KANE JAMES J. MURPHY MARVIN L. LADDU ATUL R., DONERTY JAMES F., and PULSETT JOE K The long term suppression of ventricular arrhythmia by oral acetylcholine in patients with coronary artery disease 631
- DEBIANCO ROBERT Reply 590 (Letter to Editor)
- DI SCASCIO GERMANO and TARANTA ANGELO Reply 403 (Letter to Editor)
- DONERTY JAMES F (See de Souza et al) 631
- DONOHUE DENNIS J (See Chun et al) 910
- DORHOUT MEER EVERET J (See Rado Juhos and Dorhout Mees) 183
- DORIS IAN (See Kubac et al) 277
- DRIFUS LEONARD S (See Naito et al) 34
- DUFFY G J (See Farrell and Duffy) 134
- DUNCAN W J (See Burns Culham and Duncan) 177

F

- ELDAR MICHAEL (See Shoenfeld et al) 179
- ELHARRAR VICTOR (See Zipes et al) 1006
- ELIOT ROBERT J (See Buell and Eliot) 771
- ELKAYAM URI and FRISHMAN WILLIAM Cardiovascular effects of phenothiazines 357
- ESCOBINAS ANFARO J (See Mochos et al) 641
- EVANS DENIS A WILFITT WALTER C. and HENNINGSEN CHARLES H Alcohol and coronary heart disease 584 (Annot)

F

- FARRELL, R J and DUFFY G J J Prophylaxis of venous thromboembolism 134 (Letter to Editor)
- FARSIDE ARDESHIR, MICHILSON FRIC L. GREEN PAV ALLAN M. SPIELMAN SCOTT R. HOROWITZ LEONARD N. and JOHNSON MARK P Repetitive responses to ventricular extra stimuli: incidence mechanism and significance 590
- FATIMI A. OLLSIFU (See Ali et al) 570
- FAZZINI P F MARCHI F. LICCI L. LEDDA F. and MUGELLI A Reply 771 (Letter to Editor)
- FEHRI, KIM (See Vlay et al) 901
- FINICI RICCARDO (See Zeppilli et al) 281
- (See Zeppilli et al) 281
- FIDELL JEFF (See Coumel and Fidell) 1073
- FINKELSTEIN STANLEY M (See Zobel et al) 81
- FISHER, MICHAEL L (See Carliner et al) 483
- FLETCHER GERALD F (See John Ion and Fletcher) 63
- FOLGER GORDON M JR NARRAH HANI M. and STEIN PAUL D Evaluation of the anatomy of congenitally malformed aortic valves by endocardial catheterization 17
- FORSEFELL, GUNILLA (See Nyquist et al) 1007
- FRERI F (See Henderson and Freri) 91
- FRISHMAN WILLIAM (See Elkayam and Frishman) 357
- FRUKU YUICHI (See Hambe et al) 13
- (See Hibi et al) 69

G

- GAGNON ROGER M (See Morissette et al) 319
- GALLACHER JOHN J (See Mitchell McNamara and Gallacher) 173
- GANDHI AGHAWINKAR (See Minchoo et al) 647
- GARDIKAS CONSTANTINE D (See Cokkinos et al) 87
- GASCHING GIANNI (See Caruzzo et al) 270
- GEORGEACU CONSTANTIN (See Cotranimion et al) 69
- GRACE JOSEPH E (See Wilson et al) 10
- GILMORE ROBERT C JR (See Zipes et al) 10
- GILBERT LITTON (See Vignato et al) 782

- DALEN JAMES F (See Hada et al) 871
- DAVEY PETER W (See Hada et al) 871
- DAVIA JAMES E (See Chun et al) 910
- DEAN H (See Hada et al) 871

toxicities associated with the use of these agents. The incidence of these phenomena is likely to increase with the recent approval of daunorubicin for treatment of adult nonlymphocytic leukemia by the FDA so their information is timely.

In their report however Henderson and Frei state that cyclophosphamide (CTX) when used in large single doses has caused acute mild pericarditis. The fact of the matter is that CTX in large doses (144 to 200 mg/kg) used prior to bone marrow transplantation has caused death from severe refractory myocardial failure. Signs of CTX cardiomyopathy include loss of R waves and ST T wave changes on the ECG. However interpretation of these findings is difficult because they are nonspecific and frequently transient. The incidence of ECG changes at doses of 150 mg/kg of CTX appears to be approximately 70%. Also elevation in serum myocardial enzymes (Ch, SGOT and LDH) has been observed at approximately a 40% frequency with the same dose. Overt congestive heart failure did not occur at this dose.

When compared with anthracycline cardiomyopathy CTX effects appear to be different. CTX cardiomyopathy has an acute onset with death occurring from intractable heart failure in reported cases within 15 days of the initial dose. The effects are dose-related but do not appear to be the cumulative result of long term drug administration. Cardiac morphology at autopsy is characterized as hemorrhagic myocardial necrosis which may be focal with fibrin microthrombi in capillaries and interstitial fibrin deposition. An exudative nonmalignant pericardial effusion is usually present in addition to pulmonary edema and ventricular hypertrophy. A proposed mechanism of CTX cardiotoxicity is direct endothelial damage leading to extravasation of blood containing high concentrations of drug which subsequently produces myocardial cell damage, fibrin precipitation and focal hemorrhage with development of refractory congestive heart failure. Unlike anthracycline cardiotoxicity, no risk factors for CTX cardiomyopathy have yet been identified.

As more is learned about marrow transplantation and the aggressive nature of conditioning regimens using high doses of chemotherapeutic agents increases the frequency of many untoward effects including cardiotoxicity is also likely to increase.

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Reply

To the Editor

We agree completely with the comment made by Dr Roberts in the above letter. In fact the sentence which quotes from our article represent a typographical error in the original submitted manuscript which was not picked up by multiple proofreadings. The error statement is: Applebaum and associates in the quoted reference have been that single doses have caused acute myocardial failure instead of mild pericarditis. We appreciate Dr Roberts bringing this point to the attention of readers because we too feel that it is an important point.

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Effects of antiarrhythmics in ischemic models

To the Editor

We read with interest Levites and Anderson's paper concerning the electrophysiological effects of disopyramide during myocardial ischemia. They and several other authors have shown local anesthetic antiarrhythmics to possess degrees of selective electrical depression in ischemic models. As postulated by Levites and Anderson, nonuniform drug distribution within myocardial tissue may be an important explanation of selective depression of ischemic tissue by antiarrhythmic drugs. We would like to offer a working model regarding altered antiarrhythmic availability to the ischemic myocardium.

As a result of ischemia, normal myocardial substrate utilization is transformed to anaerobic glycolysis with an ensuing intracellular acidosis. The magnitude of the acidosis in the extracellular space exceeds that of extracellular fluid with intracellular pH dropping below 6.0. Recent information seems to show that local anesthetic antiarrhythmic actions are dependent upon an active ionized form and their ability to gain entrance to an intracellular site of action. Because local anesthetics are weak bases and considering the intracellular acidosis present in the ischemic myocardium, Kupersmith and colleagues theorized a higher degree of intracellular ioniza-

- GALICIA, EMILIO R. (See Wilson et al.) 689
GOLDFAR, D. (See Weber et al.) 764
GOLDSTEIN SIDNEY (See Alam and Goldstein) 517
GOODNIGHT SCOTT H., JR., PANTLEY GEORGE A., AND RAHIMTOOLA SHAHRUDIN H. Antithrombotic therapy for asphenous vein bypass grafts, 546 (Annot.)
GOBELS ANTON P. (See Wellens et al.) 934
GORLIN RICHARD (See Ambrose et al.) 433
— (See Kunkle et al.) 813
GOTSMAN MERVYN B. (See Lewis et al.) 490
GRABOWSKI GREGORY A. (See Bass et al.) 807
GRAUBUS THOMAS II (See DeSilva et al.) 881
GREENBLATT DAVID J. (See Ochs et al.) 341
GREENHALGH R. M., ILLINGWORTH R. D., McFIE, J., MILLS S. P., PERKINS G. D., AND ROSE F. CLIFFORD Extracranial to intracranial microvasculature for the treatment of completed ischemic stroke 937 (Annot.)
GREZANSKY ALLAN M. (See Farshidi et al.) 59
GREZANDER E., KEIDAR, S., AND PALANT A. Serum myoglobin as a sensitive index of myocardial infarction 945 (Letter to Editor)
GRITTEN JERRY C., MASON JAY W., AND CALFFE RICHARD V. Clinical use of an implantable automatic tachycardia terminating pacemaker 1093
GROSSMAN RICHARD S., CAPOVE ROBERT J., AND MOST ALBERT S. Reply 765 (Letter to Editor)
GROSSMAN STANLEY J. (See Lee and Grossman) 41
GURET PASCAL (See Wyatt et al.) 821
GUTEL TURKAN Anomalous ECG and PCG recordings, "68 (Letter to Editor)
GULEWICKY, VICTOR. (See Pandian Kosowsky and Gurewicz) 847
- H
- HADA YOSHITAKI, WOLFE, CARLA MURRAY GORDON F., AND CRAIG ERNEST Right ventricular myofascia. Case report and review of phonocardiographic and auscultatory manifestations 871
HAFFMAN ZAREH (See Horn et al.) 1037
— (See Young et al.) 1041
HAFIZATZ CHARLES I., ALPERT JOSEPH S., AND DALFIN JAMES E. Tocainide for refractory ventricular arrhythmias of myocardial infarction 1013
HAGAN A. D. (See Lutz et al.) 349
HADAD BENYAD (See Moschos et al.) 647
HAMID AHMADIBIS DEMETRIOS ISKANDRIAN ABDULMASSIH S., SEGAL, BERNARD L., MINTZ, GARY S. AND BENNIS CHARLES H. Angina pectoris and coronary artery disease in patients with severe aortic valvular disease 441
HALL JUDITH G. (See Paul, Hall, and Wilson) 761
HAMBY ROBERT I., PRAKASH M. N., WYNE, UZAIR A., AND HOFFMAN IRWIN Electrocardiographic left ventricular hypertrophy and coronary artery disease: clinical, hemodynamic and angiographic correlations, 794
HANPTON J. R. Reply 408 (Letter to Editor)
HANCOCK E. WILLIAM. On the elastic and rigid forms of constructive pericarditis, 917
HANEDA TAKASHI MIURA YUKIO ARAI TOHRU NAKAJIMA, TOSHIYUKI MIURA TAKUJI HONMA TAKAO KOBAYASHI KIYOSHI SAKUMA HISACHI ADACHI MARU MIYAZAWA KOZU NUREPUNAGA JAORU AND TAKISHIMA TAMOTSU Norepinephrine levels in the coronary sinus in patients with cardiovascular diseases at rest and during isometric handgrip exercise 465
HARRISON DONALD C., WINKLE ROGER SAMI MAGDI AND MASON JAY Encainide: A new and potent antiarrhythmic agent 1046
— (See James J. Mason, and Harrison) 1031
HERGEN, JAMES J. (See Zipes et al.) 1055
HEMONAS ELIAS T. (See Cockings et al.) 802
- HELLEN HAPPEK P. (See Markov et al.) 639
HENDERSON I CRAIG AND FREI E. III Reply 947 (Letter to Editor)
HENG MING A. (See Wan et al.) 81
HENNEMANN CPABLE H. (See Evans Willett and Hennemann) 54
HERMAN MICHAEL V. (See Ambrose et al.) 433
— (See Kunkle et al.) 813
HIMI NORIO FUKUI YO CHI NISHIMURA KINYA MIWA, APATA KAMBE, TADASHI AND SAKAMOTO NOBLO Cross sectional echocardiographic study on persistent left superior vena cava 63
— (See Karbe et al.) 53
HIGGIN S. B. (See Ryden et al.) 15
HILLIS W. (See Bastian et al.) 1017
HIRATA TSUNOBU (See Sunagawa et al.) 89
HIROTA YASUO (See Hirohara et al.) 4
HISANAGA ASARO (See Hisanaga et al.) 60
HISANAGA KOZO HISANAGA ASARO NAGATA KAZUHIKO NIJIKIE YO HIYASU Transoesophageal cross sectional echocardiography, 60
HIYOSHI YUCHI OMAE TEPIO HIPOITA YASUO TAKE-HI TA MORIKIUE IKEDA KAZUO NAKANO MASAHITO TANAKA SEIJI IKEDA HISAO AND KATSUKI SHIPANO LAI Clinicopathological study of the heart and coronary arteries of autopsied cases from Japan and coronary artery wave in the precordial leads, 41
HJ EN J. H. MITA C. LIN. Left vectorcardiography in adults. Part 2, 3
— (See Humpby et al.) 34
HJ ANI S. DAN (See Ryden et al.) 1005
HJ ONO S. KAMBE ET AL.) 3
HJ LI F. C. NYMAN F. (See Szlavay et al.) 3, 3
— (See Merz and Hollenberg) 33
HJ NN TAKA (See Haneda et al.) 462
HJ NN EDWARD R. HADIADIAN ZAREH JOHNSON JEANNE L., VA ALLO HELEN G., WILLIAMS JOHN H., AND JOYCE MICHAEL D. Safety evaluation of tocainide in the American Evaluation Use Program 103
— (See Young et al.) 1041
HJ RWITY LEONARD N. (See Farshidi et al.) 59
HO MA MITSUMOTO (See Tomoda et al.) 306
HOTTA TETSUHI (See Saito and Hotta) 866
HOW JACQUES STRACHAN RONALD W. AND BEWSHER, PETER D. Giant cell arteritis—a cardiological blind spot 405 (Annot.)
HULTGREN HERBERT N. (See Shettigar and Hultgren) 590
HUNDER, CENE G. (See Huston and Hunder) 99
HUSTON KEVIN A. AND HUNDER, GENE G. Giant cell (cranial) arteritis: a clinical review 99
HUTCHINS GROVER M. (See Silverman and Hutchins) 230
— (See Moore et al.) 610
HUTTON I. (See Bastian et al.) 1017
- I
- ICHIE YOSHIYASU (See Hisanaga et al.) 605
ICHIMIZU SATOSHI (See Kambe et al.) 53
IKAHEIMO MARKKU J. Mitral prosthetic dehiscence and paraprosthetic regurgitation 940 (Letter to Editor)
— (See Hyosho et al.) 474
IKEDA HISAO Hemodynamic and electrophysiologic interactions between antiarrhythmic drugs and beta blockers with special reference to tocainide 1076
ILLINGWORTH, R. D. (See Greenhalgh et al.) 937
IMAZUMI TSUTOMU Arrhythmias in sleep apnea 513
INCE ALEXANDRU (See Coton et al.) 763
ISKANDRIAN ABDULMASSIH S. (See Hakki et al.) 441
- J
- JACOBS GLENN P., AND PORES, IRA H. Aprindine psychosis, 347

Table I

| Agent | Acid/base | pKa | % ionized at pH 7.4 | % ionized at pH 6.0 |
|--------------|-----------|------|---------------------|---------------------|
| Quinidine | Base | 8.34 | 90 | 99 |
| Procainamide | Base | 9.24 | 98 | 99 |
| Disopyramide | Base | 8.36 | 90 | 99 |
| Lidocaine | Base | 7.86 | 13 | 99 |

tion of the antiarrhythmic. Thus the availability of active cationic antiarrhythmic to an intracellular receptor site may improve.

Table I shows the pKa and percent ionized at pH 7.40 (physiologic) and pH 6.0 (ischemic intracellular space) for several local anesthetic antiarrhythmics. The percentage ionized of disopyramide increases to nearly 100% in an acid media. Quinidine and procainamide show similar changes with lidocaine changing most in percent ionized from physiologic to acid pH. In publications investigating these antiarrhythmics it appears that the degree of selectivity in ischemic tissue parallels the change in percent of drug ionized expected to be available in the intracellular space.

Further studies similar to Levites and Anderson's are certainly warranted to elucidate effects of antiarrhythmics in ischemic model. We believe the physicochemical properties of specific local anesthetic antiarrhythmics remain the key to understanding the concept of selective depression of ischemic tissue.

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Serum myoglobin as a sensitive index of myocardial infarction

To the Editor

We read with great interest the article of Tommaso Salcedo and Klutz concerning CK and myoglobin in myocardial infarction. We disagree however with their statement that myoglobin is an insensitive marker of myocardial necrosis in its early phase because of its lack of appearance in 50% of their patients having definite acute myocardial infarction.

We have recently examined 15 patients with acute myocardial infarction, seven with diaphragmatic infarction and eight with anteroapical infarction. In all patients frequent blood samples were drawn for determination of serum myoglobin, total CK and CPK-MB isoenzyme (7 samples for each marker during 50 hours).

Total CK determination was performed according to the method of Rosalki. The CK-MB fraction was detected by electrophoresis on cellulose acetate plates. For the measurement of CK-MB a densitometric method was used by scanning the electrophoretic fraction of MB with the quick scan fluorimeter. The amount of CK-MB was calculated as a percent of the total CK activity. Serum myoglobin levels were determined by radioimmunoassay using a kit from Nucleon Medical Systems Inc., Newport Beach, California.

We found that significantly elevated serum myoglobin indicative of infarction was present 3 hours following the onset of chest pain in all patients examined and predicted elevations of total CPK and CK-MB by 6 to 12 hours. Utilizing the sensitive radioimmunoassay for detection of myoglobin, we found no evidence for the staircase phenomenon previously described.

The interval during which the myoglobin assay remained elevated following infarction was found to be up to 50 hours (mean 37 hours), somewhat longer than previously described (mean 24 hours). On comparing patients with diaphragmatic infarction (group A) to those with anteroapical infarction (group B), we found significant differences in the myoglobin time curves. A five-hour plateau observed only in group B patients. However, the interval during which myoglobin was elevated was longer in group A patients by about 33 hours.

A time sensitivity curve was drawn for myoglobin and CK-MB which showed that serum myoglobin preceded CK-MB for the 50% sensitivity time (by three hours) and for the 100% sensitivity time (by six hours) (Fig. 1).

None of the patients serving as the control group had elevated CK-MB, total CK, or serum myoglobin levels above normal.

- JALIFF J AND ANTZELEVITCH C Pacemaker annihilation diagnostic and therapeutic implications 128 (Annot.)
- JANSENS W J (See Vanhoutte and Janssens) 263
- JEWITT DAVID E Hemodynamic effects of newer antiarrhythmic drugs, 984
- JOHN T JACOB (See Chandy John and Cherian) 578
- JOHNSON JEANNE L (See Horn et al) 1037
- (See Young et al) 1041
- JOHNSTON BARBARA AND FLETCHER GERALD F Reply 763 (Letter to Editor)
- JONES DANIEL (See Bury and Jones) 591
- JONES N L (See Oldridge LaSalle and Jones) 755
- JONES RICHARD L (See York et al) 267
- JOSEPHSON MARK E (See Farshidi et al) 59
- JOSKOWICZ G (See Weber et al) 764
- JUCHOWSKA EVA (See Rado Juhos and Dorhout Mees) 183
- JUMP DAVID A (See Ragg et al) 581
- K
- KAINDL K (See Weber et al) 764
- KAISER, LENHART KAISER, PETER KARLSSON JAN AND ROSSNER, STEPHAN Beta blockers and running 943 (Letter to Editor)
- KAISER, PETER (See Kaiser et al) 943
- KAMBE TADASHI ICHIMIYA SATOSHI TOGUCHI MASAO HIBI NORIO FUKUI YOICHI NISHIMURA KIYUA SAKAMOTO NOBUO AND HOJO YASUO Apex and subapical approaches to Ebstein's anomaly using cross-sectional echocardiography 3
- (See Hibi et al) 69
- KANAZAWA MASAKUNI (See Vyden et al) 590
- KANP JAMES J (See de Soya et al) 631
- KARONIT LINDA M (See Ragg et al) 581
- KARLSSON JAN (See Kaiser et al) 943
- KATO TADAYUKI (See Sugiyama et al) 829
- KATSUKI SHIBANOSUKE (See Hivosh et al) 424
- KALL UPENDRA ARORA RAMESH AND RANI SUDHA Uhl's anomaly with rudimentary pulmonary valve leaflets A clinical hemodynamic angiographic and pathologic study 673
- KAWADA SHIAKI (See Tomoda et al) 306
- KELDER M (See Grenadier Heider and Palant) 948
- KERSHNER RICHARD E (See Venkatesh et al) 302
- KERIN NICHOLAS Z Reply 134 (Letter to Editor)
- KHAN ABDUL HAKIM Spontaneous resumption of sinus rhythm after prolonged AF 409 (Letter to Editor)
- KI PING F (See Moore et al) 610
- KIKUCHI YUTAKA (See Sunagawa et al) 89
- KIMIRIS DEMETRIOS (See Hakkio et al) 441
- KLINK W J Treatment of primary pulmonary hypertension 88 (Annot.)
- KOBAYASHI KIYONORI (See Haneda et al) 465
- KOHDF SHIPONAKAL (See Tomoda et al) 306
- KOLFF NIKOLAI S Evaluation of contractile state of the left ventricle from the peak of the first derivative of the apexcardiogram 600
- KONING GERHART VEEFKIND ADRIAAN H. AND SCHNEIDER HANS Cardiac damage caused by direct application of defibrillator shocks to isolated Langendorff perfused rabbit heart 473
- KOSOWSKY BERNARD D (See Pandian Kosowsky and Gurewich) 84
- KRALIOS ALEXANDROS C (See Bugni et al) 657
- KRITZ ANDRES (See Suarez et al) 678
- KULBAC GREGORY DORIS IAN ORODO MILENA AND DAVEY PETER W Malignant granular cell myoblastoma with metastatic cardiac involvement Case report and echocardiogram 2
- KUIDA HIROSHI (See Bugni et al) 657
- KULBERTUS H F (See Walz et al) 788
- KUNKER STEVEN H RICHARD ALBERTO D SMITH HARRY JR. CORLEIN RICHARD HOFFMAN MICHAEL V. AND KUPFI WITH JEFFERSON S. Segment deviations and extent of coronary artery disease 813
- KUPFERSMITH JOEL (See Kunk et al) 813

L

- LADDU ATUL R (See de Soya et al) 631
- LAIRD J D Thomas Young (1713-1829) 1
- LAKS MICHAEL M (See Barrett et al) 211
- LAUREUX JACQUES (See Morissette et al) 319
- LANGOU RENE A VAN DYKE CRAIG TAHAN STEVEN R. AND COHEN LAWRENCE S Cardiovascular manifestations of tricyclic antidepressant overdoses 458
- LANIADO SHILOMO (See Rotmensch et al) 419
- LAP CEES (See Simoons Lap and Pool) 9
- LA SALLE D (See Oldridge LaSalle and Jones) 755
- LATTING CLIFTON A AND SILVERMAN MARK E Acute myocardial infarction in hospitalized patients over age 70 311
- LAWRIE T III V Comparison of newer antiarrhythmic agents 990
- LEATHAM AUBREY AND BRIGDEN WALLACE Reply 941 (Letter to Editor)
- LEBACQZ E G (See Chaudron and Lebacz) 131
- LEDDA F (See Fazzini et al) 211
- LEGRAND V (See Waleffe et al) 788
- LEHAN PATRICK H (See Markov et al) 779
- LEHER CARL V (See Unverferth et al) 699
- LEMIERE JEAN (See Morissette et al) 319
- LESTER EVA Common sense and clinical chemistry 170 (Annot.)
- LESTER LUCILLE A (See Cabin Lester and Roberts) 571
- LEVINE HERBERT J Difficult problems in the diagnosis of chest pain 108
- LEVY MORRIS J (See Shoensfeld et al) 111
- LEWIS BASIL S LEWIS NOGA SPOZNENIKOV DAN AND GOTSMAN MERVYN S Isovolumic relaxation period in man 490
- LEWIS NOGA (See Lewis et al) 490
- LEWIS RICHARD P (See Unverferth et al) 699
- LICHSTEIN EDGAR Site of origin of ventricular premature beats in patients with mitral valve prolapse 44
- LIE J T AND GROSSMAN STANLEY J Pathology of the heart in acromegaly anatomic findings in 9 autopsy patients, 41
- OLNEY BYRON A. AND SPITTELL JOHN A Perioperative hypertensive crisis and hemorrhagic diathesis Fatal complication of clinically unsuspected pheochromocytoma 716
- LIRON MEIR (See Rotmensch et al) 419
- LOYD BRIAN L (See Ochs et al) 341
- LONG WILLIAM B. AND COFFIN SIDNEY The digestive tract as a cause of chest pain 567
- LOPEZ EMICIDIO A (See Liplinger and Lopez) 597
- LOWY BERNARD (See DeSilva et al) 881
- LUTZ J F HAGAN A D VIVFEC W A R THOMPSON S J AND AARON M L "Pseudo-tumor" of the right ventricular outflow tract and congenital pulmonary valve regurgitation A case report 341
- LYONS CHALMERS Site of functional right bundle branch block 637
- M
- MACCARTHY E PAUL (See Stokes Oates and MacCarthy) 741
- MACFARLANE I W (See Bastien et al) 101
- MAGORIN RAYMOND D (See Unverferth et al) 622
- MALCOLM ALASDAIR D Myocardial infarction around the mitral leaflet prolapse 71 (Annot.)
- MALCOLM DANIEL L (See Ah et al) 579
- MALLIANI ALBERTO SCHWARTZ PETER J AND ZANCHETTI ALBERTO Neural mechanism in life-threatening arrhythmias 703
- MALONEY JAMES D NICHOLSON ROGER G. AND MCCOLLUM J M Open clinical studies at a referral center Chronic maintenance treatment of patients with recurrent sustained ventricular tachycardia refractory to conventional antiarrhythmic agents 1023
- MANDAL, WILLIAM J (See Barrett et al) 211

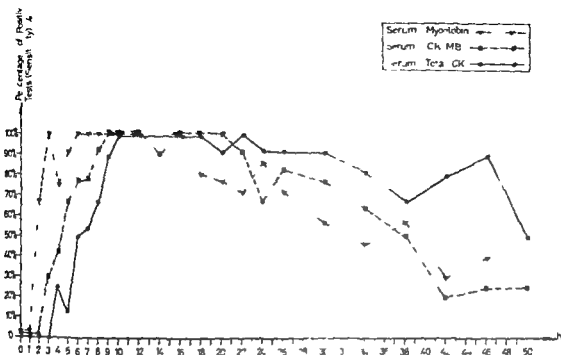


Fig 1 Time (hours) sensitivity curve of serum myoglobin, total CK, and CK-MB isoenzyme of patients examined.

values (for total CK ≥ 10 IU, for CK-MB isoenzyme less than 1% of total CK, for myoglobin ≥ 50 ng/cc). It is apparent though that myoglobin is a very sensitive indicator of myocardial infarction and since it decreases to normal levels rather quickly it can serve as a valuable aid in the diagnosis of reinfarction and infarct extension. CK-MB is also a sensitive indicator of myocardial infarction and has the additional quality of high specificity. Thus these assays combined will provide a most sensitive and specific early indicator of acute myocardial infarction.

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Reply

To the Editor

The work of Grenadier, Keidar, and Palant is appreciated. Our evidence would tend to agree with theirs concerning the sensitivity of a myoglobin rise as an indicator of myocardial necrosis. In our patients reported, all of whom were found to have enzyme evidence and ECG criteria consistent with transmural infarcts, there was a detectable rise in serum myoglobin concentration. This suggests that at least in this small group of patients, a myoglobin rise is indeed sensitive for the presence of myocardial necrosis.

This is consistent with the accumulated experience which has found a 75 to 100% rate of increased serum myoglobin in comparison with other indicators of myocardial necrosis.

Of interest is their finding of elevated serum myoglobin levels at only 15 hours following the onset of the clinical event. Although it has been reported that myoglobin concentration will begin to rise within two hours after the ligation of a canine coronary artery, previous work suggests this may not be the case in humans. In our group there were four patients who did not have elevated myoglobin levels when sampled upon arrival in the emergency room. In our group sampling was done an average of 2.5 hours following the onset of symptoms, and the average time from symptoms to first detectable myoglobin elevation was almost four hours. This yields a sensitivity of 50% as an early indication of myocardial infarction in patients who were selected because of ECG evidence of transmural infarctions. This is in agreement with the data of Gökenson and associates, who found myoglobin elevation in only 40% of patients seen in an emergency room who subsequently had evidence of myocardial necrosis.

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- MARCHI F (See Fazzini et al) 271
- MARDELLI T JOSEPH MORGANROTH JOEL, NAITO MASAHITO AND CHEN CHIN C Cross sectional echocardiographic detection of aortic valve prolapse 293
— (See Naito et al) 34
- MARR, HERBERT (See Schweitzer and Marr) 119
— (See Schweitzer and Marr) 255
- MARRIS JOHN E (See Come et al) 593
- MARROW ANGEL H, OGLETHORPE NICOL C, BLAKE THOMAS M, LEHAN PATRICK H AND HILLIAMS HARPER K Hemodynamic electrocardiographic and metabolic effects of fructose diphosphate on acute myocardial ischemia 619
- MARROR BRUCE M AND BLACK MARTIN M Unusual manifestations of severe sick sinus syndrome 95
- MARRA, SEBASTIANO (See Paolillo et al) 761
- MARTINEZ ELLOGIO E (See Ambrose et al) 433
- MARTINEZ, JOSÉ A (See Suárez et al) 678
- MARTINS JAMES H (See Venkatesh et al) 302
- MARY RABINE L (See Waleffe et al) 788
- MARZILLI MARIO (See Sabbah, Marzilli, and Stein) 77
- MASON JAY W (See Griffin, Mason and Colfee) 1003
— (See Winkle, Mason and Harrison) 1031
— (See Harrison et al) 1048
- MATSUMURA SEIYA (See Tomoda et al) 306
- MATTHEW WILLIAM D (See Walker and Matthew) 896
- MAVIC ZARKO Mitral valve prolapse syndrome 409
(Letter to Editor)
- MCCABE, COLIN (See Come et al) 523
- MCCLOY JAMES (See McCloy and McCloy) 933
- MCCLOY R. F. AND MCCLOY JAMES Autoaddiction: a hypothesis on hunger and obesity 933 (Annot)
- MCCOLGAN J. M (See Maloney, Nissen and McColgan) 1023
- MCIE, J (See Greenhalgh et al) 937
- MCLACHLAN J. H (See Bastian et al) 1017
- MCNAMARA JAMES O (See Pritchett, McNamara and Gallagher) 683
- MEERBAM SAMUEL (See Wyatt et al) 891
- MEGGS LEONARD G AND HOLLENBERG NORMAN K When is loss of responsiveness to a vasodilator agent in the patient with congestive heart failure due to tachyphylaxis? 53
- MELARA, JOSÉ (See Ambrose et al) 433
- MENON DEVIDAS (See York et al) 967
- MEYER, JERRY F (See Wasserman, Meyer and Ross) 500
- MICELI DOMENICO (See Viorio et al) 787
- MICHELSON ERIC L (See Farshidi et al) 59
- MICKLE ELAINE (See Vyden et al) 590
- MILES S. P (See Greenhalgh et al) 937
- MINTZ, GARY S (See Hakki et al) 441
- MIR, M. A Reply 271 (Letter to Editor)
- MIROWSKI M, MOWER, MORTON M AND REID PHILIP R The automatic implantable defibrillator 1089
- MITCHELL, WINSTON A (See Romanelli et al) 617
- MIZRA, TAKUJI (See Haneda et al) 465
- MIZRA, YUKIO (See Haneda et al) 460
- MIZRA, ARATA (See Hibi et al) 69
- MIZUJAWA, KOZUJI (See Haneda et al) 465
- MOERL, H. (See Su et al) 339
- MOLLER, JAMES H (See Bass et al) 807
- MOORE, G WILLIAM HUTCHINS GROVER M, BULKLEY BERNADINE M, TSENG JENNIFER S AND KIPING F Constituents of the human ventricular myocardium: Connective tissue hyperplasia accompanying muscular hypertrophy 610
- MOREIRA EDUARDO AND ALDAY LUIS E Phenolamine and IHSS 134 (Letter to Editor)
- MORGANROTH JOEL (See Naito et al) 34
— (See Marzilli, Morganroth, Naito and Chen) 295
- MORISSETTE MARTIN GAGNON ROGER M, LAMOREUX JACQUES AND LEMIRE JEAN Effects of angiographic contrast media on colloid oncotic pressure 319
- MORTENSEN OLE (See Ryden et al) 1006
- MORTON J. J (See Taylor, Baum and Morton) 93.
- MOSCHOS CHRISTOS H HAIDER BUNYAD ESCOBINAS AMPARO J, GARDHI ASHWINKUMAR AND RFGAN TIMOTHY J Chronic use of a piro versus indomethacin during non thrombotic myocardial ischemia: effects on survival 617
- MOST ALBERT S (See Grodman, Capone and Most) 765
- MOWER MORTON M (See Mirowski, Mower and Reid) 1089
- MUGELLI A (See Fazzini et al) 271
- MUJAS SALES K (See Sawawa, Mujas and Armenian) 144
- MURPHY MARVIN L (See de Soyza et al) 631
- MURRAY GORDON F (See Hada et al) 871
- MURRAY THOMAS F (See Ragg et al) 581
- N
- NAGATA KAZUHIRO (See Hisanaga et al) 60.
- NAITO MASAHITO, MORGANROTH JOEL, MARDELLI T JOSEPH AND CHIN CHIN C Rheumatic mitral stenosis: cross-sectional echocardiographic analysis 31
- (See Marzilli et al) 29
- NAKAJIMA TOSHIYUKI (See Haneda et al) 460
- NAKAMURA MOTOOMI (See Sunagawa et al) 89
- NAKANO MASAHIRO (See Hiyoshi et al) 44
- NARANG PREM H (See Carliner et al) 483
- NAVARRO-LOPEZ FRANCISCO (See Betriu et al) 223
- NAZARIAN IRAJ (See Shalibi, Reyhani and Nazarian) 767
— (See Alipour, Tarbiat and Nazarian) 809
- NICHOLS DONALD R (See Wilson et al) 689
- NISHIMURA KIYUA (See Kambe et al) 53
— (See Hibi et al) 69
- NISSEN ROGER G (See Maloney, Nissen and McColgan) 1023
- NIXON P. G The responsibility of the cardiologist mapmak or 139
- NORDLANDER ROLF (See Nyquist et al) 1000
- NOYES RUSSELL JR (See Venkatesh et al) 302
- NYQUIST OLOF FORSELL, GUNILLA, NORDLANDER ROLF AND SCHENCK GUSTAFSSON HARIH Hemodynamic and antiarrhythmic effects of tocainide in patients with acute myocardial infarction 1000
- O
- OATES HELEN F (See Stokes, Oates and MacCarthy) 741
- OATES J. A (See Roden et al) 15
- OCHS HERMANN R, GREENBLATT DAVID J, LLOYD BRIAN L, WOO ELAINE, SONNATG M AND SMITH THOMAS W Entry of quinidine into cerebrospinal fluid 341
- OGLETHORPE NICOLE C (See Markov et al) 639
- OKADA RYOZO (See Takagi and Okada) 838
- OLDRIDGE N. B., LASALLE D. AND JONES N. L Exercise rehabilitation of female patients with coronary heart disease 700 (Annot)
- OLNEY BYRON A (See Lie, Olney and Spittell) 716
- OLSEN E. G. J The pathology of idiopathic hypertrophic subaortic stenosis (hypertrophic cardiomyopathy): A critical review 503
- OMAE TERUO (See Hiyoshi et al) 474
- ONDRO MILENA (See Kubac et al) 227
- OPTE LIOVEL H Myocardial infarct size: Part 1. Basic considerations, 355
— Myocardial infarct size: Part 2. Comparison of anti infarct effects of beta blockade, glucose, insulin, potassium, nitrates and hvaluronidase 531
- ORITA YASUHIRO (See Sunagawa et al) 89
- OSTER KURT A Reply 945 (Letter to Editor)
- OZAWA TAKATKAI (See Sugiyama et al) 829
- P
- PALANT A (See Grenadier, Keidar and Palant) 948
- PANDIAN NATASA G, KOSOWSKY BERNARD H AND GUREWICH VICTOR Transferrable temporary pacing and deep vein thrombosis 847

This discrepancy may be due to the difficulty in timing of the onset of an out of hospital clinical event rather than the sensitivity of the assay which has been most reliable and quite accurate

The statement that use of early sampling is relatively insensitive is hence based on comparison to confirmatory ECG changes and was intended to discourage the use of myoglobin as an emergency room screening tool. However, I do concur with Grenadier and co-workers' assessment that serial myoglobin determinations may be potentially useful as a guide to determining episodes of reinfarctions or infarct extension in patients with acute infarction.

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- PANSINI R (See Cocco et al) 878
 PANTLEY GEORGE A (See Goodnight Pantley and Rahim toola) 586
 PAOLILLO VITO MARRA SEBASTIANO SPADACCINI FELICE AND ANGELINO PIER FEDERICO Dynamic electrocardiographic recording during sexual activity in recent post myocardial infarction and revascularization patients 763 (Letter to Editor)
 PAPAZOGLU NICHOLAS M Sex and the differential diagnosis of uncomplicated angina pectoris 410 (Letter to Editor)
 PAULI RICHARD M HALL JUDITH G AND WILSON KATH LEEN M Risks of anticoagulation during pregnancy 761 (Annot)
 PAULS DAVID L (See Venkatesh et al) 302
 PERELMAN M AND SHIU M F Migration of redundant pacing electrode 591 (Letter to Editor)
 PERKIN G D (See Greenhalgh et al) 937
 PEROSIO ALBINO M (See Suarez et al) 678
 PETER, ROBERT H (See Rubin and Peter) 757
 PHAF BOB (See Wellens et al) 934
 RICHARD AUGUSTO D (See Ambrose et al) 433
 — (See Kunkes et al) 813
 PICKUP J C A new approach to improved metabolic control in diabetics Continuous subcutaneous insulin infusion 417
 PINKHAS JACK (See Shoenfeld et al) 179
 — (See Berliner et al) 134
 PIPBERGER, HUBERT V AND LOPEZ, ENIGDIO A Silent subendocardial infarcts fact or fiction? 597
 PIRRAMI MARCO MARIA (See Zeppilli et al) 281
 — (See Zeppilli et al) 213
 PISCIONE FEDERICO (See Vigorito et al) 782
 PLOTNICK, GARY D (See Carliner et al) 483
 PODRID PHILIP J (See DeSilva et al) 881
 POOL JAY (See Simoons Lap and Pool) 9
 PORES IRA H (See Jacos and Pores) 347
 PRAKASH M N (See Hamby et al) 794
 PRITCHETT EDWARD L C MCNAMARA JAMES O AND GALLAGHER JOHN J Arrhythmogenic epilepsy and hypohypothesis 683
 PRYSTOWSKY ERIC N (See Zipes et al) 1005
 PUCCI P (See Fazzini et al) 271

R

- RADO JANOS P JUHOS EVA, AND DORHOUT MEES EVERT J Renal response to graded intravenous hypertonic NaCl infusion in healthy and hypertensive subjects dose-related impairment in distal NaCl reabsorption 183
 RAE, A P (See Bastian et al) 1017
 RAGG KERRY E MURRAY THOMAS F., KARBONIT LINDA M AND JUMP DAVID A Errors in predicting function al capacity from a treadmill exercise stress test 581 (Annot)
 RAHMTOOLA SHAHRUDIN H (See Goodnight Pantley and Rahimtoola) 586
 RAJFER, SOL I (See Chun et al) 940
 RAMIRIZ ALBERTO (See Come et al) 523
 RAMSDALE, D R AND BENNETT D H Asymmetric septal hypertrophy in conditions other than HISS 931 (Annot)
 RANI SUDHA (See Saul Afara and Rani) 673
 REELE S H (See Roden et al) 15
 REGAN TIMOTHY J (See Moschos et al) 647
 REID PHILIP R (See Mrowka Mower and Reid) 1089
 REITZ GERO Reply 522 (Letter to Editor)
 REYHANI FATEMEH (See Shikhi R Shani and Nazarian) 767
 ROBERTS RAYMOND W Cyclophosphamide cardiomyopathy 917 (Letter to Editor)
 ROBERTS WILLIAM C (See Chahrestani and Roberts) 563
 RODEN S H, REELE S H AND ARR H KEITH SMITH H F OATY A AND VOOLEY H L Tocainide therapy for refractory ventricular arrhythmias 1

- ROMANELLI RENZO WILLIS WILLIAM H JR MITCHELL, WINSTON A, AND BOUCEK ROBERT J Coronary arteriograms and myocardial scintigrams in the electrocardiographic syndrome of septal fibrosis 617
 RONFELD ROBERT A Comparative pharmacokinetics of new antiarrhythmic drugs 9/8
 ROSE F CLIFFORD (See Greenhalgh et al) 937
 ROSE HAROLD H (See Vyden et al) 590
 ROSS ALLAN M (See Wasserman Meyer and Ross) 400
 ROSS M ALISON AND STREETER, DANIEL H JR Rupture of myocardium and mitral valve replacement 840 (Letter to Editor)
 ROSSNER, STEPHAN (See Kayser et al) 943
 ROTMENSCH HESCHI H, LIRON MEIR, TLILSKI MARCEL, AND LANIADO SHLOMO Possible association of pneumonitis with amiodarone therapy 417 (Letter to Editor)
 RUBIN LEWIS J AND PETER ROBERT H Primary pulmonary hypertension new approaches to therapy 753 (Annot)
 RYDÉN LARS ARNMAN KRISTER CONRADSON THOR BERN HOFVENDAH, STEFAN MORTENSEN OLE AND SMEDGARD PETER Prophylaxis of ventricular tachyarrhythmias with intravenous and oral tocainide in patients with and recovering from acute myocardial infarction 1006
 S
 SABBAN HANI N., MARZILLI MARIO AND STEIN PAUL D Intracardiac phonocardiography in experimental left ventricular cavity obliteration potential clinical applicability for the distinction of obstructive cardiomyopathy 77
 — (See Folger Sabbah and Stein) 152
 SACAS BARRY (See Come et al) 573
 SAITO REIKO AND HOTTA FUTSUNI Congenital pericardial defect associated with cardiac incarceration case report 866
 SAKAMOTO NOBUO (See Kambe et al) 53
 — (See Hibi et al) 69
 SAKUMA HISAICHI (See Haneda et al) 465
 SAMI MAGDI (See Harrison et al) 1048
 SAMUEL, PAUL Drug treatment of hyperlipidemia 678
 SANDLER, GERALD The importance of the history in the medical clinic and the cost of unnecessary tests 928 (Annot)
 SANDS MURRAY P (See Hu et al) 339
 SANTAMORE WILLIAM P WALINSKY PAUL BOVE ALFRED A, COX ROBERT H., CAREY RITA A AND SPANN JAMES F The effects of vasoconstriction on experimental coronary artery stenosis 85
 SANZ, GINES (See Betru et al) 293
 SAPOZNIKOV DAN (See Lewis et al) 490
 SASSARA MASSIMO (See Zeppilli et al) 213
 — (See Zeppilli et al) 281
 SAWAYA JABER I MUJAIN SALIM K AND ARMENIAN RAHOUTYAN K Early diagnosis of pericarditis in acute myocardial infarction 144
 SCHAEFER, O Lo the poor Eskimo? 914 (Letter to Editor)
 SCHAMMOOTH LEO The clinical use of intravenous verapamil 1070
 SCHENCK GUSTAFSSON KARIN (See Nyquist et al) 1000
 SCHLAG W (See Biannino et al) 191
 SCHMITZ, H (See Wink and Schmitz) 677
 SCHNEIDER HANS (See Koning Veefkind and Schneider) 473
 SCHROEDER, R (See Biannino et al) 191
 SCHUSTER, EDWARD H, AND BULKLEY BERNADINE H Ischemic cardiomyopathy A clinicopathologic study of fourteen patients 306
 SCHWARTZ, PETER J (See Malliani, Schwartz, and Zanchetti) 705
 SCHWEITZER, PAUL, AND MARK HERBERT The effect of atropine on cardiac arrhythmias and conduction Part I 119
 — AND — The effect of atropine on cardiac arrhythmias and conduction Part 2, 255

Book reviews

Neural Mechanisms in Cardiac Arrhythmias Edited by Peter J Schwartz, Arthur M Brown, Alberto Malliani and Alberto Zanchetti. New York 1978. Raven Press. 460 pages. Price \$35.00.

This publication contains reports presented in Florence during 1978 on not only an important aspect of cardiology but on some much neglected aspects of cardiology. The role of the central nervous system and the autonomic nervous system in the regulation of the central and peripheral circulation is clearly and succinctly reviewed by the many contributors to this publication. The investigators in Milan, Italy, have been responsible in large part for the symposium. Among the subjects discussed are arrhythmias, sudden death, electrophysiology as influenced by the nervous system, cardiac reflexes, baroreceptors and pharmacology. The many papers are well illustrated and the references are carefully selected. This is an excellent publication which certainly should interest all cardiologists and trainees in cardiology.

British Medical Bulletin Smooth Muscle Edited by E Bulbring and T B Bolton. London 1979. The Medical Dept. The British Council. 107 pages. Price \$12.50.

This is an excellent issue of the *Bulletin*. The physiology and function of smooth muscle are clearly described. A great deal of the discussions are devoted to vascular smooth muscle

Physicians and certainly physiologists, who are concerned with vascular physiology will find it extremely profitable to study this issue and even to own a copy for future reference. The many contributors have done an outstanding job in summarizing the recent extensive advancements in knowledge of smooth muscle in this September 1979 issue of the *British Medical Bulletin*.

Advances in Cardiovascular Physics. Volume 1. Theoretical Foundations of Cardiovascular Processes Edited by D N Chiba, F Van Vollenhoven, W J Yang and H Reul. Basel. Switzerland 1979. S. Karger AG. 183 pages. Price \$64.00.

This is the first volume of *Advances in Cardiovascular Physics*. The volume should interest physicists, bioengineers and physiologists involved in the biophysical interpretation of cardiovascular phenomena. Among the subjects discussed are electrophysiology of the heart, biomechanics of blood flow, biotransport mechanisms and thermoregulation. Clinicians will understand this series of publication, but a perusal of the publication will clearly indicate the intricacies of the various phenomena which clinicians so casually take for granted. Physicists will find the publications to be extremely readable but will quickly learn the intricacies and complexities of biologic processes. This is a good publication to initiate a much needed aspect of cardiovascular con-

current research and the practice of medicine.

Books received

Coronary Heart Surgery: A Rehabilitation Measure Edited by H Rookkamm and M Schimzigger. Seacaucus, N.J. 1979. Springer-Verlag. New York. Inc. 394 pages. Price \$42.90.

Skin Deep: The Makings of a Plastic Surgeon By Donald T McVishan, M.D. and Shirley Hartman. Boston 1979. Little Brown & Company. 339 pages. Price \$10.00.

Clinical Cardiology By Maurice Sokolow, M.D. and Malcolm B McIlroy, M.D. Los Altos, Calif. 1979. Lange Medical Publishers. 718 pages.

Primary Care Judgments of Nurses and Physicians. Vol. 4. Reliability and Validity Research Report By Frank M McLaughlin, John W Carr and Kevin L Delucchi. San Francisco 1979. Veterans Administration Medical Center. 70 pages.

Microcirculation—Volume 1 Edited by Gabor Kaley and Burton L Altura. Baltimore 1979. University Park Press. 598 pages. Price \$44.50.

Monographs on Atherosclerosis. Part 9. Clinical Methods in the Study of Cholesterol Metabolism Edited by David Kritchevsky and O J Pollak. Written by H S Dodhu, M J Rudchodkar and D T Mason. Basel 1979. S. Karger AG. 167 pages. Price \$53.00.

New Pathways in Laboratory Medicine Edited by S B Rosolki. Bern, Switzerland 1978. Hans Huber Publishers. 142 pages.

Diagnosis and Therapy of Coronary Artery Disease: Concepts and Controversies Edited by Peter F Cohn, M.D. Boston 1979. Little Brown & Company. 509 pages. Price \$32.50.

Plain Film Interpretation in Congenital Heart Disease, second edition By Leonard E Swischuk, M.D. Baltimore 1979. The Williams & Wilkins Company. 266 pages. Price \$28.50.

- LEGAL, BERNARD L. (See Hakki et al.) 441
- ELTZER, CARL C Smoking and coronary heart disease: what are we to believe? 240
- SHABET, JAMI G RYFMANI, FATEMIH AND NAZARIAN, IRAS Ratios of septum and LV free wall in IHSS and HCM 66 (Letter to Editor)
- SHEPARD, ROY J Exercise and recurrence of myocardial infarction 404 (Annot.)
- SHETGIRAR, UDIPI R AND HULTGREN, HERRBERT N Correlation between exercise hemodynamics and increased magnitude of 1 terminal force 590 (Letter to Editor)
- SHU, M F (See Perelman and Shiu) 591
- SHOBACK, DOLORES (See Vlay et al.) 907
- SHOENFELD, YEHUDA, FIDAR, MICHAEL, BEDAZOVSKY, BENI, LEVY, MORRIS J AND PINKHAS, JACK Aortic stenosis associated with gastrointestinal bleeding: A survey of 612 patients 19
- (See Berliner et al.) 134
- SHOTS, AKURA (See Tomoda et al.) 306
- SHIVASTAYA, SAVITRI (See Bass et al.) 807
- SILVERMAN, GERTRUDY (See Zonerach, Silverman and Zonerach) 34
- SILVERMAN, KENNETH J AND HUTCHINS, GROVER M Infarct expansion: the second event after acute myocardial infarction 230 (Clinical pathologic conference)
- SILVERMAN, MARK F (See Latting and Silverman) 311
- SHOONS, MAARTEN, LAP, CFFS AND POOL, JAN Heart rate levels and ventricular ectopic activity during cardiac rehabilitation 9
- SHON, ANARJIT Reply 768 (Letter to Editor)
- SHVEDGARD, PETER (See Rydin et al.) 1006
- SMITH, HARRY JR. (See Hunkes et al.) 813
- SMITH, R. F. (See Roden et al.) 15
- SMITH, THOMAS W. (See Ochs et al.) 341
- STAG, M. (See Ochs et al.) 341
- ACCINI, FELICE (See Paolillo et al.) 763
- N JAMES F. (See Santamore et al.) 856
- LMAY, SCOTT R. (See Farshidi et al.) 69
- PELL, JOHN A. (See Lee, Olive and Spittell) 16
- TE, NORTON Diet in the treatment of hyperlipidemia 94
- KEE, BRIAN J. (See York et al.) 267
- N PAUL D. (See Sabbah, Marzilli, and Stein) 7
- (See Folger, Sabbah and Stein) 152
- WACH, K. (See Weber et al.) 764
- VART, I. McD. G. Limited pressure control to "optimum" levels may reduce the rate of myocardial infarction in hypertensive subjects, 402 (Annot.)
- ES GORDON S. OATES, HELEN F. AND MACCARTHY, E. PAUL. Antihypertensive therapy: New pharmacological approaches, 741
- ICHAN, RONALD W. (See How, Strachan and Bewsher) 405
- ETER, DANIEL II JR. (See Ross and Streeter) 946
- DEI, C. (See Cocco et al.) 878
- JADY V. AMORY, DAVID W. SANDS, MURRAY P. AND MORRI, H. Effects of circulatory arrest and resuscitation on regional blood flow during surface induced hypothermia 332
- AZZ, LUIS D. KREITZ, ANDRES, ALVAREZ, JOSE A. MARTINEZ, JOSE A. AND PEROSIO, ALBINO M. Dissimilar atrial rhythms: A patient with triple right atrial rhythm 678
- YAKA, SATORI, OZAWA, TAKAYUKI, KATO, TADATYUKI AND SUZUKI, SHOICHI Recovery time course of ventricular vulnerability after coronary reperfusion in relation to mitochondrial function in ischemic myocardium 829
- YAFARA, KENJI, ORITA, YASUHIKO, TANAKA, SENICHI, KIKUCHI, YUTAKA, NAKAMURA, MOTOYUKI AND HIRATA, TSUNEO Left atrial ball thrombus diagnosed by two-dimensional echocardiography 80
- TOY, JOHN R. AND BAR, OR, ODED Thermal illness in fun running 78
- YUJI, SHOICHI (See Sugiyama et al.) 879

SZLAVY, LASZLO, ADAMS, DOUGLASS F. HOLLENBERG, NORMAN H. AND ABRAMS, HERBERT L. Cardiac lymph and lymphatics in normal and infarcted myocardium 373

T

- TAGAWA, RYUSUKE (See Tomoda et al.) 306
- TAHAN, STEVEN R. (See Langou et al.) 48
- TAKACI, TATSUJI AND OKADA, RYOZO An electrocardiographic-pathologic correlative study on left axis deviation in hypertensive hearts 838
- TAKESHITA, MORIYUKI (See Hiyoshi et al.) 424
- TAKISHIMA, TAMOTSU (See Haneda et al.) 46
- TANAKA, SEIJI (See Hiyoshi et al.) 474
- TANAKA, SEINICHI (See Sunagawa et al.) 89
- TARANTA, ANGELO (See DiSciscio and Taranta) 943
- TARBIAT, CYAVOLSH (See Alipour, Tarbiat and Nazarian) 89
- TAYLOR, K. M. BAIN, H. W. AND MORTON, J. J. The role of angiotensin II in the development of peripheral vasoconstriction during open heart surgery 930 (Annot.)
- TEICHHOLZ, LOUIS E. (See Ambrose et al.) 433
- THOMPSON, RODNEY L. (See Wilson et al.) 689
- THOMPSON, S. I. (See Lutz et al.) 349
- TOGUCHI, MASAO (See Kambic et al.) 53
- TOMIYASO, CARL L. Reply 949 (Letter to Editor)
- TOMODA, HARUO, HOSHIAI, MITSUMOTO, TAGAWA, RYUSUKE, HOIDE, SHIRO, AKU, KAWADA, SHIAKI, SHOTS, AKIRA AND MATSUYAMA, SEIYA Evaluation of left atrial thrombus with computed tomography 306
- TRONI, WALTER (See Caruzzo et al.) 20
- TSAGARIS, THEOFILIS J. (See Burgi et al.) 657
- TSARTSALIS, GEORGE D. (See Kokkinos et al.) 802
- TSENG, JENNIFER S. (See Moore et al.) 610
- TUBAU, JULIO (See Betru et al.) 223
- TUPILSKI, MARCEL (See Rotmensch et al.) 412

U

- UEDA, HAZLO (See Hiyoshi et al.) 424
- UNDERFERTH, DONALD V. MACGRIEN, RAYMOND D., LEWIS, RICHARD P. AND LFER, CARL V. Long term benefit of dobutamine in patients with congestive cardiomyopathy 677

V

- VANAGT, EDGAR J. (See Wellens et al.) 934
- VAN DYKE, CRAIG (See Langou et al.) 48
- VANHOUTTE, P. M. AND JANSSENS, V. J. Thermosensitivity of cutaneous vessels and Raynaud's disease 263 (Annot.)
- VAN VALKENBURG, CHARLES (See Venkatesh et al.) 302
- VASSALLO, HELEN G. (See Horn et al.) 1037
- (See Young et al.) 1041
- VEEFKIND, ADRIAAN H. (See Koning, Veeffkind and Schneider) 473
- VENKATESH, ALAGIRISWAMI, PALLS, DAVID L., CROWE, RAYMOND, NOTES, RUSSELL, JR., VAN VALKENBURG, CHARLES, MARTINS, JAMES II AND KERBER, RICHARD E. Mitral valve prolapse in anxiety neurosis (panic disorder) 302
- VIEWEG, W. V. R. (See Lutz et al.) 349
- VIGORITO, CARLO, BETOCCHI, SANDRO, BONZANI, GILLIO, GUIDICE, PIETRO, MICELI, DOMENICO, PISCIONE, FEDERICO AND CONDORELLI, MARIO Severity of coronary artery disease in patients with diabetes mellitus: Angiographic study of 34 diabetic and 120 nondiabetic patients 787
- VINE, HUGH S. (See Come et al.) 23
- VLAY, STEPHEN C. BLUMFELT, DAVID S., SHOBACK, DOLORES, FENIK, KIM AND BULKLEY, BERNADINE H. Delayed acute myocardial infarction after blunt chest trauma in a young woman 907

International Symposium on Myocardial Hypertrophy

An International Symposium on Myocardial Hypertrophy sponsored by the American Section of the International Society for Heart Research will be held in Burlington Vermont on June 14 through 17 1981 For further information contact Dr Norman Alpert Professor of Physiology College of Medicine University of Vermont Burlington Vt 05401

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Workshops of the American Section of the International Society for Heart Research will be held in Burlington Vermont on June 17 through 20 1981 For further information contact Dr Norman Alpert Professor of Physiology College of Medicine University of Vermont Burlington Vt 05401

Conference and Symposium on Cardiac Arrhythmias

The Second Teaching Conference and Symposium on Cardiac Arrhythmias entitled Mechanisms of Sudden Death

will be held on June 15 through 19 1981 in Florence Italy The conference is sponsored by the Department of Medicine University of Oklahoma and by the Instituto di Ricerche Cardiovascolari of the University of Milan For further information contact Dr Benjamin J Scherlag Veterans Administration Medical Center 971 N E 13th St Oklahoma City Okla 73104 Telephone (405) 271-4747

1981 Subspecialty Examination in Cardiovascular Disease

Beginning in 1981 the American Board of Internal Medicine's Subspecialty Examination in Cardiovascular Disease will revert to the former fall date The pertinent dates for 1981 are

Registration Period January 1 1981 to April 1 1981

Examination Date November 10 1981

Deadline for Cancellation October 1 1981

For application forms contact American Board of Internal Medicine 3624 Market St Philadelphia Pa 19104 Telephone (215) 243 1500

Author index

VYDEN JOHN V., ALPERN HARVEY L., KANAZAWA MASAHU
NI MICKLE ELAINE AND ROSE HAROLD H. Func-
tion testing soon after acute myocardial infarction
590 (Letter to Editor)

W

WALEFFE A. MARY RABINE L. LEGRAND V., DEMOULIN J.
CL. AND KULBERTUS H. E. Combined mexiletine
and amiodarone treatment of refractory recurrent
ventricular tachycardia 788

WALINSKY PAUL. (See Santamore et al.) 852

WALKER, DAVID H. AND MATTERN WILLIAM E. Rickettsial
vasculitis 896

WASSERMAN ALAN G. MEYER, JERRY F. AND ROSS ALLAN
M. The relationship of pulmonary artery wedge
pressure to the posterior aortic wall echocardi-
ogram in patients free of obstructive mitral valve
disease 500

WEBER, H. STEINBACH K. JOSEKOWICZ G. GLOGAR D. AND
KAINDL K. TTM versus Holter monitoring of
symptomatic arrhythmias 764 (Letter to Editor)

WELD FRANCIS M. (See Bigler and Weld) 1081

WELLES HEIN J. J. GORGELS ANTON P. BRAAT SIMON J.
BAR FRITS W., VANAGT EDGAR J. AND PHAF
BOB. Effect of oral disopyramide on serum digoxin
levels. A prospective study 934 (Annot.)

WESSFL, H. J. (See Bismuno et al.) 191

WILLIAMS ADRIAN J. Reply 944 (Letter to Editor)

WILLIAMS JOHN H. (See Horn et al.) 1037

WILLIETT WALTER C. (See Evans Williett and Hennekens)
584

WILLIS WILLIAM H. JR. (See Romanelli et al.) 617

WILSON KATHLEEN M. (See Paul Hall and Wilson) 761

WILSON WALTER R. NICHOLS DONALD H. THOMPSON
RODNEY L. GULLIANI EMILIO R. AND GERACI
JOSEPH E. Infective endocarditis: therapeutic con-
siderations 689

WINK A. AND SCHMITZ H. Cytomegalovirus myocarditis
67

WINKLE ROGER A. MASON JAY W. AND HARRISON DONALD
C. Tocainide for drug resistant ventricular ar-
rhythmias. Efficacy, side effects and lidocaine
responsiveness for predicting tocainide success,
1031

— (See Harrison et al.) 1046

WOLFE CARLA. (See Hada et al.) 871

WOOD ELAINE. (See Ochs et al.) 341

WOOSLEY H. L. (See Roden et al.) 15

WYATT HORACE L., MEERBAUM SAMUEL, HONG MING A.
GUERET PASCAL, AND CORDAY ELIOT. Cross-
sectional echocardiography III. Analysis of geo-
metric models for quantifying volume of symmetry
and asymmetric left ventricles, 821

WYNE UZAIR A. (See Hamby et al.) 794

Y

YAMAGUCHI IWAO. (See Barrett et al.) 23

YORK ERNEST L. JONES RICHARD L. SPROLL BRIAN J.
AND MENON DEVIDAS. Management of neonatal
polycythemia with hypoxic lung disease 44
(Annot.)

YOSHINAGA KAORU. (See Haseeda et al.) 46

YOUNG MICHAEL D. (See Horn et al.) 103

— HADIDIAN Z. HORN H. JOHNSON J. AND VASSALLO R.
Treatment of ventricular arrhythmias with oral
tocainide 1041

Z

ZANCHETTI ALBERTO. (See Malliani, Schwartz, and Zanchetti)
70

ZEFFILLI PAOLO, FERRARI MARCO M. CASARARA MARINO
AND FENICI RICCARDO. T wave abnormalities in
top ranking athletes: effects of isoproterenol stimu-
lation and physical exercise 213

— FENICI RICCARDO, CASARARA MASSIMO, FERRARI MARCO
MARIA AND CASELLI GIOVANNI. Wenckebach
second-degree A-V block in top ranking athletes: an
old problem revisited 281

ZIPES DOUGLAS P., ELHARRAR VICTOR, GILMOLAR ROBERT
G. JR., HEGER JAMES J. AND PRYSTOWSKY JACOB N.
Studies with aprindine 1033

ZOBEL, LARRY R. FINKELSTEIN STANLEY M. CARLILE
PETER F. AND COHN JAY N. Pressure pulse con-
tour analysis in determining the effect of vasodila-
tor drugs on vascular hemodynamic impedance
characteristics in dogs 81

ZONERACH OLGA. (See Zonerach, Silverman and Zonerach)
754

ZONERACH SAMUEL, SILVERMAN GERTHELE AND ZONERACH
OLGA. Primary myocardial disease and diabetes
mellitus, and small vessel disease 44 (Annot.)

formed on 41 acromegalic patients at Mayo in the 60 year period 1919 to 1978 of which 27 cases with adequate clinical data and tissue were included in this pathologic review of the heart in acromegaly. Cardiomegaly was common (22 of 27 cases or 81%) and occurred in both hypertensive and nonhypertensive patients. The mean heart weight (618 g) of 16 patients who died 10 or more years after the clinical onset of acromegaly was significantly higher ($p < 0.01$) than that (348 g) of 11 patients who died within 10 years of the clinical onset of the disease. Disproportionate cardiomegaly (compared to visceromegaly) occurred in about one fourth to one third of the cases. The enlarged hearts seldom exceeded 200% (that is twice) of the expected heart weights according to the patient's body weight and body length. Apart from hypertension other conditions to which cardiomegaly in acromegaly has been attributed were uncommon in our series: diabetes 15% (four of 27), significant coronary artery disease 11% (three of 27), and valvular heart disease 19% (five of 27). Myocardial hypertrophy (93% or 25 of 27) and interstitial fibrosis (85% or 23 of 27) were constantly observed. Other histological findings which have not been noted in earlier studies included lymphomononuclear cell infiltrate or myocarditis (59% or 16 of 27) and small vessel disease of the myocardium (22% six of 27). Although controversial, the possibility of a specific acromegalic cardiomyopathy cannot be discounted on the basis of the currently available evidence.

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Subject Index*

A

- tolol, oral, long term suppression of ventricular arrhythmia by in patients with coronary artery disease (de Souza et al.) 631
- comment to reviewers, 73
- cardiovascular disease psychosocial and behavioral influences in the pathogenesis of (Buell and Eliot) 73
- pathology of the heart in anatomic findings in autopsied patients (Lue and Grossman) 41
- tion of NTG (Brady and Berghuis) 409 (Letter to Editor)
- clinical vectorcardiography in. Part 1 (Hoffman) 239
- Part 2 (Hoffman) 33
- trial fibrillation prolonged, spontaneous resumption of sinus rhythm after (Khan) 409 (Letter to Editor)
- antiarrhythmic, encainide a new and potent (Harrison et al.) 1046
- new comparison of (Lawrie) 990
- and coronary heart disease (Evans Willett and Hennkens) 94 (Annot)
- Emergency Use Program safety evaluation of tocamide in the (Horn et al.) 103
- lalone and mexiletine combined treatment for refractory recurrent ventricular tachycardia (Waleffe et al.) 68
- he treatment of cardiac arrhythmias in children one hundred thirty five cases (Coulmel and Fidélie) 1063
- possible association of pneumonitis with (Rot mensch et al.) 412 (Letter to Editor)
- a, of senile (Burch) 407 (Annot)
- left ventricular hypertrophy versus (Burns Culham and Duncan) 76 (Letter to Editor)
- Reply (Singh) 76
- pectors and coronary artery disease in patients with severe aortic valvular disease (Hakki et al.) 441
- ef of by periartrial muscle resection of myocardial bridges (Betrui et al.) 223
- complicated, sex and the differential diagnosis of (Papazoglou) 410 (Letter to Editor)
- graphic contrast media on colloid oncotic pressure effects of (Morissette et al.) 319
- ensin II role of in the development of peripheral vasoconstriction during open heart surgery (Taylor Bain and Morton) 93 (Annot)
- lation, pacemaker diagnostic and therapeutic implications (Jalife and Antzelevitch) 128 (Annot)
- ments 138 274 416 594 77 92
- alous ECG and PCG recordings (Gurel) 68 (Letter to Editor)
- Reply (Basta) 76

- Antiarrhythmic(s) a vent(s) conventional, chronic maintenance tocamide therapy in patients with recurrent sustained ventricular tachycardia refractory to open clinical studies as a referral center (Malorev, Brown, and McCollan) 1023
- encainide a new and potent (Harrison et al.) 1046
- new comparison of (Lawrie) 990
- and hemodynamic effects of tocamide in patients with a late myocardial infarction (Nyquist et al.) 1011
- drugs and beta blockers hemodynamic and electrophysiologic interactions between, with special reference to tocamide (Ikram) 1076
- new comparative pharmacokinetics of (Ronfeld) 978
- newer hemodynamic effects of (Jewitt) 94
- in ischemic models effects of (Bauman, Curtis and Covin) 94 (Letter to Editor)
- Anti coagulation during pregnancy risks of (Pauli, Hall, and Wilson) 71 (Annot)
- Antidepressant overdose tricyclic cardiovascular manifestations of (Langou et al.) 405
- Antihypertensive therapy new pharmacological approaches (Stokes, Oates, and MacCarthy) 41
- Anti infarct effects of beta blockade glucose-insulin potassium, nitrates, and hyaluronidase comparison of Part - of Myocardial infarct size (Opie) 531
- Antithrombotic therapy for asphenous vein bypass grafts (Goodnight, Pantley, and Rahimtoola) 44 (Annot)
- Anteroventricular (panic disorder) mitral valve prolapse in (Venkatesh et al.) 30
- Aortic root, echocardiographic pattern of motion of the a., a correlate of left atrial volume changes (Bianco et al.) 191
- hemodynamic correlates of late diastolic posterior motion of the (Ambrose et al.) 433
- stenosis associated with gastrointestinal bleeding. A survey of 61 patients (Shoenfeld et al.) 179
- valvula congenitally malformed, evaluation of the anatomy of by on-line-view aortography (Folger Sabbah, and Stein) 15
- porcine stenotic echocardiographic features of (Alam and Goldstein) 17
- prolapse cross-sectional echocardiographic detection of (Mardelli et al.) 90
- valvular disease severe angina pectoris and coronary artery disease in patients with (Hakki et al.) 441
- wall echocardiogram, posterior relationship of pulmonary artery wedge pressure to the in patients free of obstructive mitral valve disease (Wasserman, Meyer and Ross) 50
- Aortography on-line-view evaluation of the anatomy of congenitally malformed aortic valves by (Folger Sabbah, and Stein) 15
- Apex and subphrenic approaches to Eisenstein anomaly using cross-sectional echocardiography (Kambe) 33
- Apexcardiogram, first derivative of the title state of the left ventricle (Kolev) 600
- Apnea, sleep arrhythmias in (

- 1 blood flow during surface induced hypothermia effects of circulatory arrest and rewarming on (Su et al.) 337
- Resurgator congenital pulmonary valve "pseudo-tumor" of the right ventricular outflow tract and a case report (Lutz et al.) 349
- periparturient mitral prosthetic dehiscence and (Ikahori et al.) 340 (Letter to Editor)
- Reply (Chun et al.) 340
- Rehabilitation, cardiac heart rate levels and ventricular ectopic activity during (Summons, Lap and Pool) 3
- Relaxation period in man isovolumic (Lewis et al.) 490
- Renal response to graded intravenous hypertonic NaCl infusion in healthy and hypertensive subjects: dose-related impairment in distal NaCl reabsorption (Radd, Juhos, and Mees) 183
- Repetitive responses to ventricular extrastimuli: incidence mechanism and significance (Farshidi et al.) 59
- Reerton, peritranal muscle of myocardial bridges: relief of angina by (Betrui et al.) 223
- Revere capacity left ventricular O₂ consumption and coronary blood flow following coronary occlusion, effect of arterial pressure on (Bugni et al.) 657
- Responsibility of the cardiologist mapmaker the (Nixon) 139
- Responsiveness, loss of to a vasodilator agent in the patient with congestive heart failure when is it due to tachyphylaxis? (Meggs and Hollenberg) 753 (Annot.)
- Resuscitation, cardiopulmonary—an element of sophistication in the 18th century (Bartecchi) 590 (Annot.)
- multibacterial infectious hazards of (Achong) "39 (Annot.)
- Retinal vein thrombosis, central in a patient with primary pulmonary hypertension (Berliner et al.) 134 (Letter to Editor)
- Reversal and circulatory arrest effects of on regional blood flow during surface-induced hypothermia (Su et al.) 332
- Rheumatic fever in children on (Aryanpur Kashani) 942 (Letter to Editor)
- Reply (DiSciascio and Taranta) 943
- retrograde cross-sectional echocardiographic analysis (Vento et al.) 34
- St. Joseph's dissimilar atrial. A patient with triple right atrial rhythm (Sudrez et al.) 678
- spontaneous resumption of after prolonged AF (Khanl, 409 (Letter to Editor)
- triple right atrial, a patient with dissimilar atrial rhythms (Sudrez et al.) 678
- Recurrent vasculitis (Walker and Mattern) 806
- Right atrial rhythm triple a patient with dissimilar atrial rhythms (Sudrez et al.) 678
- bundle branch block, functional site of (Lyons) 603
- ventricular congestive heart failure of (Burch) 262 (Annot.)
- endomyocardial fibrosis simulating Pheix's anomaly (Alipour Tarbut and Nazarian) 854
- myxoma. Case report and review of phonocardiographic and auscultatory manifestations (Hada et al.) 81
- Rapid and elastic forms of constrictive pericarditis, on the (Franko) 917
- Risks of aneuploidy during pregnancy (Paul, Hall, and Wilson) 61 (Annot.)
- Romano-Ward and syndrome treated by left stellectomy and vagotonic stimulation (Chaudron and Lebacqz) 131 (Annot.)
- Rout, aortic hemodynamic correlates of late diastolic posterior motion of the (Ambrose et al.) 433
- Pulmonary pulmonary valve leaflets, Uhl's anomaly with a clinical, hemodynamic angiographic and pathologic study (Kaul, Arora, and Rami) 673
- Running and beta blockers (Kauyer et al.) 943 (Letter to Editor)
- Reply (Williams) 944
- febrile illness in (Sutton and Bar Or) 778
- Rupture of myocardium and mitral valve replacement (Ross and Streeter) 946 (Letter to Editor)
- Reply (Cobbe) 946
- S
- Safety evaluation of tocanide in the American Emergency Use Program (Horn et al.) 1037
- Saphenous vein arteriovenous (of Burch) 931 (Annot.)
- hypoxia grafts antithrombotic therapy for? (Goodnight Pantley and Itahuntola) 584 (Annot.)
- Scintigrams myocardial and coronary arteriograms in the electrocardiographic syndrome of septal fibrosis (Romanelli et al.) 617
- Secondary polycythemia with hypoxic lung disease management of (York et al.) 277 (Annot.)
- Senile anemia of (Burch) 407 (Annot.)
- Septal fibrosis electrocardiographic syndrome of coronary arteriograms and myocardial scintigrams in the (Romanelli et al.) 617
- hypertrophy asymmetric in conditions other than IHSS (Hamsdale and Bennett) 931 (Annot.)
- Septum and L.V. free wall, ratios of in IHSS and HCM (Shakibi, Reyhani, and Nazarian) "68 (Letter to Editor)
- Serum digoxin levels, effect of oral disopyramide on A prospective study (Wellens et al.) 934 (Annot.)
- myoglobin as a sensitive index of myocardial infarction (Grenadier Kendar and Palant) 948 (Letter to Editor)
- Reply (Tommaro) 949
- quinidine concentration determined by a new and specific assay: relation of ventricular premature beat suppression to (Carliner et al.) 483
- "O hospitalized patients over age acute myocardial infarction in (Lattig and Silverman) 311
- Sex and the differential diagnosis of uncomplicated angina pectoris (Papazoglou) 410 (Letter to Editor)
- Sexual activity in recent post myocardial infarction and revascularization patients: dynamic electrocardiographic recording during (Aiollo et al.) 763 (Letter to Editor)
- Reply (Johnston and Fletcher) "63
- Shunt left to right, use of the echocardiogram in delineating the location of a congenital heart disease with trisomy 13 (Cabin Lester and Roberts) 873
- Sick sinus syndrome severe unusual manifestations of (Marmor and Black) 90
- Silent ST segment deviations and extent of coronary artery disease (Hunker et al.) 813
- subendocardial infarct: fact or fiction? (Pipberger and Lopez) 99
- Sinus rhythm, spontaneous resumption of after prolonged AF (Khanl, 409 (Letter to Editor)
- syndrome sick severe unusual manifestations of (Marmor and Black) 90
- Site of functional right bundle branch block (Lyons) 603
- Sleep apnea arrhythmias in (Imazumi) 513
- Small vessel disease primary myocardial disease and diabetes mellitus (Zonerach Silverman and Zonerach) "54 (Annot.)
- Smoking and coronary disease (Burch) 421
- heart disease: what are we to believe? (Seltzer) 27
- Spontaneous resumption of sinus rhythm after prolonged AF (Khanl) 409 (Letter to Editor)
- ST segment deviations, silent, and extent of coronary artery disease (Kunkel et al.) 817
- Stellectomy left and intracavitary stimulation Romano Ward syndrome treated by (Chaudron and Lebacqz) 131 (Annot.)
- Stenosis, aortic associated with gastrointestinal bleeding: A survey of 112 patients (Shenfeld et al.) 179
- coronary artery experimental effects of vasoconstriction on (Santamoro et al.) 82
- idiopathic hypertrophic subaortic (hypertrophic cardiomyopathy) the pathology of A critical review (Gimn) 223

- Aprindine psychosis (Jacobs and Pores) 347
studies with (Zipes et al.) 1055
- Arrhythmias and the mitral valve of (Burch) 583 (Annot)
cardiac and conduction effect of atropine on Part I
(Schweitzer and Mark) 119
- Part 2 (Schweitzer and Mark) 226
in children amiodarone in the treatment of one hundred
thirty five cases (Coulmel and Fidelle) 1063
in sleep apnea (Imazumi) 513
life threatening neural mechanisms in (Malliani Schwartz
and Zanchetti) 706
symptomatic TTM versus Holter monitoring of (Weber et al.)
764 (Letter to Editor)
- Reply (Grodman Capone and Most) 765
ventricular drug resistant tocainide for efficacy side
effects and lidocaine responsiveness for predicting
tocainide success (Winkle Mason and Harrison) 1031
- in acute myocardial infarction placebo controlled study
of prophylaxis of (Campbell) 995
long term suppression of by oral acebutolol in patients
with coronary artery disease (de Soya et al.) 831
- refractory of myocardial infarction tocainide for (Haffa
jee Alpert and Dalen) 1013
tocainide therapy for (Roden et al.) 15
treatment of with oral tocainide (Young et al.) 1041
- Arrhythmic epilepsies an hypothesis (Pritchett McNa
mara and Gallagher) 683
- Arterial pressure effect of on left ventricular O consumption
coronary blood flow and reserve capacity follow
ing coronary occlusion (Bugni et al.) 657
- Arteriograms, coronary and myocardial scintigrams in the
electrocardiographic syndrome of septal fibrosis
(Romanelli et al.) 617
- Artero-occlusive atherosclerotic vein of (Burch) 931 (Annot)
Arteritis giant cell—a cardiological blind spot? (How Stra
chan and Bensher) 406 (Annot)
- (cranial) a clinical review (Huston and Hunder) 99
- Artery(ies) disease coronary and electrocardiographic left
ventricular hypertrophy clinical hemodynamic
and angiographic correlates (Hamby Irakasha
Wyne and Hoffman) 794
in patients with diabetes mellitus severity of Angio
graphic study of 34 diabetic and 120 nondiabetic
patients (Vigorito et al.) 782
long term suppression of ventricular arrhythmia by
oral acebutolol in patients with (de Soya et al.)
831
silent ST segment deviations and extent of (Kunkes et al.)
813
- tension or nor experimental effects of vasoconstriction
in (Santamore et al.) R 2
- wedge pressure pulmonary relationship of to the posterior
atrial wall echocardiogram in patients free of
bicuspid mitral valve disease (Wasserman
Ney and Rox) 400
- Apirin versus methacin chronic use of during non
the mixture myocardial ischemia effects on survival
(Moschov et al.) 64
- Asymmetric and symmetric left ventricles analysis of mathe
matic model for quantifying volume of Cross
sectional echocardiography III (Wyatt et al.)
1
- septal hypertrophy and relation to the IHSS (Ramse
dell and Benson) 100
- Atrial fibrillation and the effects of exercise (Zeppilli et al.) 11
Wenckebach second-degree in top-ranking athletes an old problem revisited (Zeppilli et al.) 281
- Atrial ball throw two-dimensional echocardiographic study (Lyon et al.) 63
- Fibrillation (AT) resumption of Letter to Editor
with Branham (Editor)
- Atrial—continued
rhythm(s) dissimilar A patient with triple right atrial
rhythm (Suárez et al.) 678
right tripartite patient with dissimilar atrial rhythm
(Suárez et al.) 68
thrombus left evaluation of with computed tomography
(Tomoda et al.) 306
volume changes left echocardiographic pattern of motion
of the aortic root as a correlate of (Bianchi et al.)
191
Atropine effect of on cardiac arrhythmias and conduction
Part 1 (Schweitzer and Mark) 119
Part 2 (Schweitzer and Mark) 226
isoproterenol and physical exercise effects of T wave
abnormalities in top ranking athletes (Zeppilli et al.)
213
A V block Wenckebach second-degree in top-ranking athletes
an old problem revisited (Zeppilli et al.) 281
Auscultatory and phonocardiographic manifestations case
report and review of in right ventricular myocardium
(Hada et al.) 81
Autosuggestion a hypothesis on hunger and obesity (McClintock
and McCloy) 933 (Annot)
Automatic implantable defibrillator the (Mirowski, Mower
and Reid) 1089
tachycardia terminating pacemaker implantable chest lead
use of an (Griffin Mason and Caffee) 1093
- B
Basic considerations of myocardial infarct size Part I of II
(Opie) 336
Beat suppression ventricular premature relation of to quinidine
concentration determined by a new and specific assay (Carliner et al.) 493
Behavioral and psychosocial influences in the pathogenesis of
acquired cardiovascular disease (Buell and Eboji) 723
Beta blockade glucose insulin potassium nitrates and bivalirudinase
comparison of antiarrhythmic effect of Part 2 of Myocardial infarct size (Opie) 531
Beta blockers and antiarrhythmic drugs hemodynamic and electrophysiologic interactions between with special reference to tocainide (Ikram) 100
and running (Hayyer et al.) 947 (Letter to Editor)
Reply (Williams) 944
clinical importance of cardioselectivity and lipophilicity in (Cruckshank) 160
Bibliographies and medical libraries, of (Bury and Jones) 591 (Letter to Editor)
Reply (Burch) 591
Bleeding gastrointestinal aortic stenosis associated with a survey of 617 patients (Shoenfeld et al.) 17
Block A V Wenckebach second-degree in top-ranking athletes
an old problem revisited (Zeppilli et al.) 281
branch, right bundle functional site of (Lyons) 63
Blood flow coronary left ventricular O consumption and reserve capacity following coronary occlusion effect of arterial pressure on (Bugni et al.) 657
regional during surface induced hypothermia effects of circulatory arrest and rewarming on (Lyon et al.) 332
Book reviews 136 213 414 533 63 91
Books received 137 213 415 533 63
Branch block right bundle functional site of (Lyons) 63
Branham sign with atrial fibrillation (Branham) 411 (Letter to Editor)
Bundle branch block right functional site of (Lyons) 63
Bypass grafts atherosclerotic vein antithrombotic therapy (Goodnight Lantley and Rahmtoola) 104
not

- Stenosis—continued
 mitral rheumatic cross sectional echocardiographic analysis (Naito et al) 34
- Stenotic porcine aortic valve echocardiographic features of (Alam and Goldstein) 517
- Stress test (treadmill exercise errors in predicting functional capacity from a (Ragg et al) 581 (Annot)
- Stroke ischemic completed extracranial to intracranial microvascularization for the treatment of (Greenhalgh et al) 937 (Annot)
- Studies with aprindine (Zipes et al) 1055
- Subaortic stenosis, hypertrophic idiopathic (hypertrophic cardiomyopathy) the pathology of A critical review (Olsen) 553
- Subcutaneous insulin infusion continuous a new approach to improved metabolic control in diabetics (Pickup) 417
- Subendocardial infarcts, "silent" fact or fiction? (Pipberger and Lopez) 597
- Subxiphoid and apex approaches to Ebstein's anomaly using cross sectional echocardiography (Kambe et al) 53
- Sudden death idiopathic mitral valve prolapse and (Anderson) 941 (Letter to Editor)
- Reply (Leatham and Brindley) 942
- Superior vena cava left cross-sectional echocardiographic study on persistent (Hibi et al) 69
- Suppression of ventricular arrhythmia long term by oral acebutolol in patients with coronary artery disease (de Souza et al) 631
- Symmetric and asymmetric left ventricles, analysis of mathematic models for quantifying volume of Cross-sectional echocardiography III (Wyatt et al) 821
- Symptomatic arrhythmias TTM versus Holter monitoring of (Weber et al) 764 (Letter to Editor)
- Reply (Grodman Capone and Most) 765

T

- T wave abnormalities in top-ranking athletes effects of isoproterenol, atropine and physical exercise (Zepilli et al) 213
- Tachyarrhythmias, ventricular prophylaxis of with intravenous and oral tocainide in patients with and recovering from acute myocardial infarction (Ryden et al) 1006
- Tachycardia terminating pacemaker implantable automatic clinical use of an (Griffin, Mason and Calfee) 1013
- ventricular recurrent sustained refractory to conventional antiarrhythmic agents chronic maintenance to tocainide therapy in patients with open clinical studies at a referral center (Maloney Nussen and McCollgan) 1023
- refractory recurrent combined mexiletine and amiodarone treatment of (Waleffe et al) 788
- Tachyphylaxis when is loss of responsiveness to a vasodilator agent in the patient with congestive heart failure due to (Meggs and Hollenberg) 73 (Annot)
- Temporary pacing transfemoral and deep vein thrombosis (Landan Kosowsky and Gurewicz) 84
- Terminal force P correlation between exercise hemodynamics and increased magnitude of (Hettiger and Hultgren) 50 (Letter to Editor)
- Reply (DiBianco) 50
- Testing, function soon after acute myocardial infarction (Ryden et al) 570 (Letter to Editor)
- Therapeutic consideration with infective endocarditis (Wilson et al) 64
- Therapy antihypertensive new pharmacological approaches (Stokes, Oates and MacFarlane) 41
- verapamil (Ahmed) 71 (Letter to Editor)
- Reply (Fazzini et al) 71

- Thermal illness in fun running (Sutton and Bar-Or) 73
- Thermosensitivity of cutaneous vessels and Raynaud's disease (Vanhoutte and Janssens) 763 (Annot)
- Thomas Young M.D. (1773-1829) (Laird) 1
- Thrombi, ventricular left echocardiographic diagnosis of (Come et al) 523
- Thromboembolism venous prophylaxis of (Farrell and Duffy) 134 (Letter to Editor)
- Thrombosis central retinal vein in a patient with primary pulmonary hypertension (Berliner et al) 134 (Letter to Editor)
- deep vein and transfemoral temporary pacing (Pandian, Kosowsky and Gurewicz) 84
- intraventricular in polycythemia vera a cause of intractable cardiac failure (Ali et al) 570
- Thrombus left atrial ball diagnosed by two-dimensional echocardiography (Sunagawa et al) 89
- evaluation of with computed tomography (Tomoda et al) 306
- Tissue hyperplasia connective accompanying muscular hypertrophy constituents of the human ventricular myocardium (Moore et al) 610
- Tocainide a prospective randomized trial of in patients following myocardial infarction (Ba-tian et al) 1017
- for drug resistant ventricular arrhythmias efficacy side effects and lidocaine responsiveness for predicting tocainide success (Winkle Mason and Harrison) 1031
- for refractory ventricular arrhythmias of myocardial infarction (Haffajee Alpert and Dalen) 1013
- hemodynamic and antiarrhythmic effects of in patients with acute myocardial infarction (Nyquist et al) 1000
- and electrophysiologic interactions between antiarrhythmic drugs and beta blockers, with special reference to (Ikram) 1016
- intravenous and oral prophylaxis of ventricular tachyarrhythmias with in patients with and recovering from acute myocardial infarction (Ryden et al) 1006
- oral treatment of ventricular arrhythmias with (Young et al) 1041
- safety evaluation of in the American Emergency Use Program (Horn et al) 1031
- success efficacy side effects and lidocaine responsiveness for predicting tocainide for drug resistant ventricular arrhythmias (Winkle Mason and Harrison) 1031
- therapy chronic maintenance in patients with recurrent sustained ventricular tachycardia refractory to conventional antiarrhythmic agents open clinical studies at a referral center (Maloney Nussen and McCollgan) 1023
- for refractory ventricular arrhythmias (Roden et al) 15
- Tomography computed evaluation of left atrial thrombus with (Tomoda et al) 306
- Torsades de pointes as a manifestation of mexiletine toxicity (Cocco et al) 84
- Toxic polyneuropathy and toxic hepatitis related to long term perphenazine maleate therapy (Caruzzo et al) 79
- (Letter to Editor)
- Reply (Nir) 271
- Toxicity mexiletine torsades de pointes as a manifestation of (Cocco et al) 84
- Tract digestive as a cause of chest pain the (Long and Cohen) 57
- Transesophageal cross-sectional echocardiography (Hassan et al) 60
- Transfemoral temporary pacing and deep vein thrombosis (Pandian Kosowsky and Gurewicz) 84
- Trauma chest blunt in a young woman delayed acute myocardial infarction after (Lay et al) 97
- Treadmill exercise stress test, errors in predicting functional capacity from a (Ragg et al) 581 (Annot)
- Treatment for primary pulmonary hypertension (Klinkel) 50 (Annot)

C

- Cardiac arrhythmias and conduction effect of atropine on Part 1 (Schweitzer and Mark) 119
 Part 2 (Schweitzer and Mark) 255
 in children, amiodarone in the treatment of one hundred thirty five cases (Coulmel and Fidele) 1063
 causalgia Horner's syndrome and the cardiac dermatome of (Burch) 938 (Annot)
 damage caused by direct application of defibrillator shocks to isolated Langendorff perfused rabbit heart (Koning Veekind and Schneider) 4.3
 dermatome cardiac causalgia and Horner's syndrome of (Burch) 938 (Annot)
 failure intractable intraventricular thrombosis in polycy-
 themia vera a cause of (Ali et al.) 520
 incarceration, congenital pericardial defect associated with case report (Saito and Hotta) 866
 involvement, metastatic with malignant granular cell myo-
 blastoma case report and echocardiogram (Kubac et al.) 227
 lymph and lymphatics in normal and infarcted myocardium (Islavy et al.) 323
 rehabilitation, heart rate levels and ventricular ectopic activity during (Simoons Lap and Pool) 9
 Cardiologic blind spot in giant cell arteritis? (How Stra-
 chan, and Bewsher) 405 (Annot)
 mapmaker the responsibility of the (Nixon) 139
 Cardiomyopathy congestive long term benefit of dobutamine in patients with (Unverferth et al.) 622
 cyclophosphamide (Roberts) 945 (Letter to Editor)
 Reply (Henderson and Frei) 947
 hypertrophic (idiopathic hypertrophic subaortic stenosis) the pathology of A critical review (Olson) 553
 ischemic a clinicopathologic study of fourteen patients (Schuster and Bulkley) 506
 Cardiopulmonary resuscitation an element of sophistication in the 18th century (Bartecchi) 580 (Annot)
 Cardioreslectivity and lipophilicity in beta blockers, the clinical importance of (Cruickshank) 160
 Cardiovascular disease(s) acquired psychosocial and behav-
 ioral influences in the pathogenesis of (Buell and Ehot) 723
 at rest and during isometric handgrip exercise norepi-
 nephine levels in the coronary sinus in patients with (Haneda et al.) 485
 effects of phenothiazines (Elkayam and Frishman) 397
 manifestations of tricyclic antidepressant overdose (Langou et al.) 458
 Cardioversion and defibrillation (DeSilva et al.) 881
 Causalgia cardiac Horner's syndrome and the cardiac der-
 matome of (Burch) 938 (Annot)
 Cavity obliteration left ventricular intracardiac phonocar-
 diography in experimental potential clinical appli-
 cability for the distinction of obliterating left ven-
 tricle from hypertrophic obstructive cardio-
 myopathy (Sabbah Mazzilli and Stern) 77
 Cell arteritis giant-a cardiologic blind spot? (How Stra-
 chan, and Bewsher) 405 (Annot)
 Central retinal vein thrombosis in a patient with primary
 pulmonary hypertension (Berliner et al.) 134 (Let-
 ter to Editor)
 Cerebrospinal fluid entry of quinidine into (Ochs et al.) 341
 Certain principles in the management of heart disease and
 pregnancy (Burch) 775
 Chemistry clinical, and common sense (Lester) 130
 Chest pain, diagnosis of difficult problems in the (Levine)
 108
 the digestive tract as a cause of (Long and Cohen) 567
 trauma, blunt in a young woman delayed acute myocar-
 dial infarction after (Vlay et al.) 907
 Children, cardiac arrhythmias vs. amiodarone in the treat-
 ment of one hundred thirty five cases (Coulmel
 and Fidele) 1063
 on rheumatic fever in (Aryapur Kasham) 942 (Letter to
 Editor)
 Reply (DiSciascio and Taranta) 943
 Chronic valvular heart disease and Coxsackie-viruses (Chan-
 dy John and Cherman) 8 (Annot)
 Circulatory arrest and rewarming effects of on regional blood
 flow during surface-induced hypothermia (Su et
 al.) 332
 Clinical chemistry and common sense (Lester) 130 (Annot)
 hemodynamic and angiographic correlates of electrocardio-
 graphic left ventricular hypertrophy and coronary
 artery disease (Hamby et al.) 794
 angiographic and pathologic study of Uhl's anomaly with
 rudimentary pulmonary valve leaflets (Kaul Aro-
 ra and Rami) 673
 use of intravenous verapamil the (Schamroth) 1070
 vectorcardiography in adults Part 1 (Hoffman) 239
 Part 2 (Hoffman) 373
 Clinicopathologic study of fourteen patients with ischemic
 cardiomyopathy (Schuster and Bulkley) 506
 of the heart and coronary arteries of autopsied cases from
 the community of Hisayama during a 10-year
 period Part IV QS waves in the precordial leads
 (Hiroshi et al.) 424
 Colloid oncotic pressure effects of angiographic contrast
 media on (Morissette et al.) 319
 Common sense and clinical chemistry (Lester) 130 (Annot)
 Comparative pharmacokinetics of new antiarrhythmic drugs
 (Ronfeld) 978
 Comparison of newer antiarrhythmic agents (Lawne) 990
 Computed tomography evaluation of left atrial thrombus
 with (Tomoda et al.) 306
 Conduction and cardiac arrhythmias effect of atropine on
 Part 1 (Schweitzer and Mark) 119
 Part 2 (Schweitzer and Mark) 255
 Congenital heart disease with trisomy 13 use of the echocar-
 diogram in delineating the location of a left
 to-right shunt (Cabin Lester and Roberts) 563
 pericardial defect associated with cardiac incarceration
 case report (Saito and Hotta) 866
 Congenitally malformed aortic valves, evaluation of the anat-
 omy of by orifice-view aortography (Folger Sab-
 bah and Stern) 157
 Congestive cardiomyopathy long term benefit of dobutamine
 in patients with (Unverferth et al.) 622
 heart failure loss of responsiveness to a vasodilator agent in
 the patient with when is it due to tachyphylaxis?
 (Meggs and Hollenberg) 253 (Annot)
 of left ventricular (Burch) 252 (Annot)
 of walking and dyspnea of (Burch) 588 (Annot)
 Constrictive pericarditis, on the elastic and rigid forms of
 (Hancock) 917
 Contour analysis pressure pulse in determining the effect of
 vasodilator drugs on vascular hemodynamic
 impedance characteristics in dogs (Zobel et al.)
 81
 Contractile state of the left ventricle from the peak of the first
 derivative of the apexcardiogram evaluation of
 (Kolev) 603
 Contrast media angiographic effects of on colloid oncotic
 pressure (Morissette et al.) 319
 Coronary arteriograms and myocardial scintigrams in the
 electrocardiographic syndrome of septal fibrosis
 (Romanelli et al.) 612
 Coronary artery(ies) and heart clinicopathological study of
 the in autopsied cases from the community of
 Hisayama during a 10-year period Part IV QS
 waves in the precordial leads (Hiroshi et al.)
 424
 disease and angina pectoris in patients with severe aortic
 valvular disease (Hakki et al.) 441
 and electrocardiographic left ventricular hypertrophy
 clinical hemodynamic and angiographic corre-
 lates (Hamby et al.) 794
 in patients with diabetes mellitus severity of Angio-
 graphic study of 34 diabetic and 120 nondiabetic
 patients (Vigoretti et al.) 782
 long term suppression of ventricular arrhythmia by
 oral acetylcholine in patients with (de Soja et al.)
 631

- Treatment—continued
 of hyperlipidemia diet in the (Spritz) 9-4
 drug (Samuel) 673
- Tricyclic antidepressant overdose cardiovascular manifestations of (Langou et al.) 438
- Triple right atrial rhythm a patient with dissimilar atrial rhythms (Suarez et al.) 678
- Trombosis congenital heart disease with use of the echocardiogram in delineating the location of a left to-right shunt (Cabin Lester and Roberts) 563
- TTM versus Holter monitoring of symptomatic arrhythmias (Weber et al.) 764 (Letter to Editor)
 Reply (Grodman, Capone and Voet) 765
- U
- Uhl's anomaly with rudimentary pulmonary valve leaflets a clinical, hemodynamic angiographic and pathologic study (Haul, Arora and Rami) 673
- Unnecessary tests cost of the importance of the history in the medical clinic and the (Sandler) 923 (Annot.)
- Unusual manifestations of severe sick sinus syndrome (Marmer and Black) 90
- V
- Vahe () aortic congenitally malformed, evaluation of the anatomy of by on-line view aortography (Folger Sabbah, and Stein) 102
- leaflets pulmonary rudimentary Uhl's anomaly with a clinical, hemodynamic angiographic and pathologic study (Haul, Arora and Rami) 673
- mitral, and arrhythmias, of the (Burch) 583 (Annot.)
- valvular aortic cross-sectional echocardiographic detection of (Vardella et al.) 290
- mitral idiopathic and sudden death (Anderson) 941 (Letter to Editor)
 Reply (Leatham and Brinden) 941
- in anxiety neurosis (panic disorder) (Venkatesh et al.) 302
- site of origin of ventricular premature beats in patients with (Lichstein) 450
- syndrome mitral (Mavric) 409 (Letter to Editor)
- regurgitation, pulmonary congenital, "pseudo-tumor" of the right ventricular outflow tract and a case report (Lutz et al.) 349
- replacement mitral, rupture of myocardium and (Ross and Streeter) 946 (Letter to Editor)
- Rep v (Cobbe) 846
- stenotic porcine aortic echocardiographic features of (Alam and Goldstein) 51
- valvular disease aortic, severe angina pectoris and coronary artery disease in patients with (Hakki et al.) 441
- heart disease chronic and Coxsackieviruses (Chandy John, and Cherian) 578 (Annot.)
- asclular hemodynamic impedance characteristics in dogs pressure pulse contour analysis in determining the effect of vasodilator drugs on (Zobel et al.) 81
- asclutis necktissal (Walker and Mattern) 896
- asoconstriction on experimental coronary artery stenosis effects of (Santamore et al.) 602
- peripheral, during open heart surgery role of angiotensin II in the development of (Taylor Bain and Morton) 970 (Annot.)
- asodilator agent loss of responsiveness to a in the patient with congestive heart failure when is it due to tachyphylaxis? (Weigs and Hollenberg) 73 (Annot.)
- drugs on vascular hemodynamic impedance characteristics in dogs pressure pulse contour analysis in determining the effect of (Zobel et al.) 81
- ectorcardiography clinical, in adults, Part 1 (Hoffman) 239
 Part 2 (Hoffman) 373
- ven arteriosclerosis, saphenous of (Burch) 931 (Annot.)
- vena cava superior left, cross-sectional echocardiographic study on persistent (Hibi et al.) 69
- Venous thromboembolism, prophylaxis of (Farrell and Duffy) 134 (Letter to Editor)
- Ventricles (s) left, contractile state of the from the peak of the first derivative of the apexcardiogram, evaluation of (Koles) 600
- obliterating from hypertrophic obstructive cardiomyopathy potential clinical applicability for the distinction of intracardiac phonocardiography in experimental left ventricular cavity obliteration (Sabbah, Marzilli, and Stein) —
- symmetric and asymmetric, analysis of mathematic models for quantifying volume of Cross-sectional echocardiography III (Watt et al.) 8-1
- Ventricular arrhythmia(s) drug-resistant, tocainide for efficacy, side effects and became responsiveness for predicting tocainide success (Winkle, Mason, and Harrison) 1031
- in acute myocardial infarction, placebo controlled study of prophylaxis of (Campbell) 980
- long term suppression of by oral sotalolol in patients with coronary artery disease (de Souza et al.) 631
- refractory of myocardial infarction, tocainide for (Haffa, Alpert, and Dalen) 1013
- tocainide therapy for (Roden et al.) 10
- with oral tocainide, treatment of (Young et al.) 1041
- congestive heart failure of right (Burch) 26 (Annot.)
- ectopic activity during cardiac rehabilitation, heart rate levels, and (Summons, Lap, and Pool) 9
- endomyocardial fibrosis, right amputating Ebstein's anomaly (Alpour Tarbiat, and Azarian) 839
- estrastimuli, repetitive responses to incidence, mechanism, and significance (Farhadi et al.) 59
- hypertrophy left electrocardiographic and coronary artery disease clinical, hemodynamic, and angiographic correlates (Hamby et al.) 74
- myocardium, human, constituents of the connective tissue hyperplasia accompanying muscular hypertrophy (Moore et al.) 610
- myxoma right, Case report and review of phonocardiographic and auscultatory manifestations (Hada et al.) 871
- outflow tract, right, "pseudo-tumor" of the and congenital pulmonary valve regurgitation, a case report (Lutz et al.) 349
- O₂ consumption, left, coronary blood flow and reserve capacity following coronary occlusion, effect of arterial pressure on (Bugni et al.) 60
- premature beats (s) site of origin in patients with mitral valve prolapse (Lichstein) 450
- suppression, relation of to serum quinidine concentration determined by a new and specific assay (Carliner et al.) 493
- rate pacing below in terminating ventricular tachycardia and flutter (Coto et al.) 763 (Letter to Editor)
- tachyarrhythmias, prophylaxis of with intravenous and oral tocainide in patients with and recovering from acute myocardial infarction (Ryden et al.) 1096
- tachycardia and flutter pacing below the ventricular rate in terminating (Coto et al.) 763 (Letter to Editor)
- recurrent sustained, refractory to conventional antiarrhythmic agents, chronic maintenance tocainide therapy in patients with, open clinical studies at a referral center (Maloney, Nissen, and McColgan) 1023
- refractory recurrent, combined mexiletine and amiodarone treatment of (Walleffe et al.) 783
- thrombi, left, echocardiographic diagnosis of (Cote et al.) 523
- vulnerability after coronary reperfusion, recovery time course of in relation to mitochondrial function in ischemic myocardium (Sugiyama et al.) 829
- Verapamil, intravenous, the clinical use of (Schamroth) 1070

Coronary artery disease—continued

- silent ST segment deviations and extent of (Kunkes et al.) 813
- stenosis experimental effects of vasoconstriction on (Santamore et al.) 802
- blood flow left ventricular O consumption and reserve capacity following coronary occlusion effect of arterial pressure on (Bugni et al.) 637
- care and mortality rates effective (Adgey) 408 (Letter to Editor)
- Reply (Hampton) 408
- disease and smoking (Burch) 421
- heart disease alcohol and (Evans Willett and Hennekens) 584 (Annot)
- and smoking what are we to believe? (Seltzer) 275
- exercise rehabilitation of female patients with (Oldridge LaSalle and Jones) 705 (Annot)
- occlusion effect of arterial pressure on left ventricular O consumption coronary blood flow and reserve capacity following (Bugni et al.) 637
- perfusion in relation to mitochondrial function in ischemic myocardium recovery time course of ventricular vulnerability after (Sugiyama et al.) 829
- mus, norepinephrine levels in the in patients with cardiovascular diseases at rest and during isometric handgrip exercise (Haneda et al.) 460
- Cost of unnecessary tests the importance of the history in the medical clinic and the (Sandler) 928 (Annot)
- Coxsackieviruses and chronic valvular heart disease (Chandy John and Cherian) 578 (Annot)
- Cranial arteritis (giant cell) a clinical review (Huston and Hunder) 99
- Cross-sectional echocardiographic detection of aortic valve prolapse (Mardelli et al.) 290
- study on persistent left superior vena cava (Hibi et al.) 69
- echocardiography III Analysis of mathematical models for quantifying volume of symmetric and asymmetric left ventricles (Wyatt et al.) 821
- transesophageal (Hisanaga et al.) 600
- Cutaneous vessels and Raynaud's disease thermosensitivity of (Vanhoutte and Janssens) 263 (Annot)
- Cyclophosphamide cardiomyopathy (Roberts) 946 (Letter to Editor)
- Reply (Henderson and Frei) 947
- Cytomegalovirus myocarditis (Wink and Schmitz) 657

D

- Damage cardiac caused by direct application of defibrillator shocks to isolated Langendorff perfused rabbit heart (Koning Veeffkind and Schneider) 473
- Death, sudden idiopathic mitral valve prolapse and (Anderson) 941 (Letter to Editor)
- Reply (Leatham and Bridgen) 942
- Deep vein thrombosis and transfemoral temporary pacing (Pandian Kosowsky and Gurewicz) 847
- Defibrillation and cardioversion (DeSilva et al.) 881
- Defibrillator automatic implantable the (Mirowski, Mower and Reid) 1089
- shocks to isolated Langendorff perfused rabbit heart cardiac damage caused by direct application of (Koning Veeffkind and Schneider) 473
- Dehiscence prothesis mitral and paraprothetic regurgitation (Ikahara) 910 (Letter to Editor)
- Reply (Chun et al.) 910
- Delayed acute myocardial infarction after blunt chest trauma in a young woman (Vlcek et al.) 30
- Derivative of the apex cardiogram first evaluation of contractile state of the left ventricle from the peak of the (holes) 611
- Dermatome cardiac arduous and (Herners van der Borch) 31
- Deviation, left axis, in the heart an electrocardiographic path (Takagi and Okada) 8

- Diabetes mellitus primary myocardial disease and small vessel disease (Zonerach, Silverman, and Aich) 704 (Annot)
- severity of coronary artery disease in patients Angiographic study of 34 diabetic and 129 nondiabetic patients (Vigorito et al.) 89
- Diabetic(s) metabolic control in new approach to continuous subcutaneous insulin infusion (Pickup) 41
- patients 34 and 170 nondiabetic patients angiographic study of Severity of coronary artery disease patients with diabetes mellitus (Vigorito et al.) 782
- Diagnostic and therapeutic implications of pacemaker substitution (Jalife and Antzelevitch) 178 (Annot)
- Diagnosis of chest pain difficult problems in the (Levine) 108
- Diastolic posterior motion late of the aortic root dynamic correlates of (Ambrose et al.) 431
- Diet in the treatment of hyperlipidemia (Spritz) 974
- Difficult problems in the diagnosis of chest pain (Levine) 108
- Digestive tract as a cause of chest pain the (Long and Colver) 567
- Digitalis and isoproterenol in younger and older individuals comparison of the inotropic action of (Cokkmes et al.) 802
- Digoxin levels serum effect of oral disopyramide on prospective study (Wellens et al.) 934 (Annot)
- Diphosphate fructose hemodynamic and metabolic effects of on acute myocardial ischemia (Markov et al.) 839
- Disopyramide oral on serum digoxin levels effect of prospective study (Wellens et al.) 934 (Annot)
- Dissimilar atrial rhythm. A patient with triple right atrial rhythm (Suarez et al.) 68
- Dobutamine in patients with congestive cardiomyopathy long term benefit of (Unverferth et al.) 611
- Drugs(1) anti arrhythmic newer hemodynamic effects of (Jewitt) 884
- new antiarrhythmic comparative pharmacokinetics (Ronfeld) 918
- resistant ventricular arrhythmias tocamide for efficacy side effects and lidocaine responsiveness for predicting tocamide success (Winkle Mason Harrison) 1031
- treatment of hyperlipidemia (Samuel) 573
- Dynamic electrocardiographic recording during sexual activity in recent post myocardial infarction and culanization patients (Paolillo et al.) 63 (Letter to Editor)
- Reply (Johnston and Fletcher) 63
- Dysfunction murmurs papillary muscle of (Burch) 1 (Annot)
- Dyspnea of congestive heart failure of walking and (Burch) 588 (Annot)

E

- Early diagnosis of pericarditis in acute myocardial infarction (Sawaya Mujum and Armanian) 144
- Ebstein's anomaly apex and subxiphoid approaches to cross sectional echocardiography (Hambe et al.) 53
- right ventricular endomyocardial fibrosis stimulating (Kopour Tarbiat and Nazarian) 811
- Echocardiogram III mode in Fabry's disease the (Rasmussen) 607
- posterior aortic wall in patients free of obstructive coronary valve disease relationship of pulmonary artery wedge pressure to (Wasserman Mever and Rasmussen) 300
- use of the in delineating the location of a left-to-right congenital heart disease with transmyocardial (Lester and Roberts) 563
- Echocardiographic analysis cross sectional of rheumatic mitral stenosis (Naito et al.) 34
- detection cross sectional of aortic valve prolapse (Mardelli et al.) 290

- Stenosis—continued
 mitral rheumatic cross sectional echocardiographic analysis (Aito et al.) 34
- Stenotic porcine aortic valve echocardiographic features of (Alam and Goldstein) 517
- Stress test treadmill exercise errors in predicting functional capacity from a (Hagg et al.) 581 (Annot)
- Stroke ischemic completed extracranial to intracranial microvascularization for the treatment of (Greenhalgh et al.) 937 (Annot)
- Studies with aprindine (Zipes et al.) 1030
- Subaortic stenosis hypertrophic cardiomyopathy (hypertrophic cardiomyopathy) the pathology of A critical review (Olson) 553
- Subcutaneous insulin infusion continuous a new approach to improved metabolic control in diabetics (Pickup) 417
- Subendocardial infarcts "silent" fact or fiction? (Pipberger and Lopez) 597
- Subxiphoid and apex approaches to Ebstein's anomaly using cross-sectional echocardiography (Kambe et al.) 3
- Sudden death, idiopathic mitral valve prolapse and (Anderson) 911 (Letter to Editor)
 Reply (Leatham and Bigden) 942
- Superior vena cava left cross-sectional echocardiographic study on persistent (Hibi et al.) 69
- Suppression of ventricular arrhythmias long term by oral acetylcholinesterase in patients with coronary artery disease (de Souza et al.) 631
- Symmetric and asymmetric left ventricles analysis of mathematic models for quantifying volume of Cross sectional echocardiography III (Wyatt et al.) 821
- Symptomatic arrhythmias TTM versus Holter monitoring of (Weber et al.) 764 (Letter to Editor)
 Reply (Grodman Capone and Most) 765
- T
- T wave abnormalities in top-ranking athletes effects of isoproterenol atropine and physical exercise (Zepilli et al.) 213
- Tachyarrhythmias ventricular prophylaxis of with intravenous and oral tocainide in patients with and recovering from acute myocardial infarction (Rydén et al.) 1006
- Tachycardia terminating pacemaker implantable automatic clinical use of an (Griffin Mason and Calfee) 1093
- ventricular recurrent sustained refractory to conventional antiarrhythmic agents chronic maintenance tocinide therapy in patients with open clinical studies at a referral center (Malonev Nassen and McCollan) 1023
- refractory recurrent combined mexiletine and amiodarone treatment of (Waleffe et al.) 88
- Tachyphylaxis when is loss of responsiveness to a vasodilator agent in the patient with congestive heart failure due to (Meyers and Hollenberg) 793 (Annot)
- Temporary pacing tran femoral and deep vein thrombosis (Landan Kosowsky and Gurewicz) 84
- Terminal force correlation between exercise hemodynamics and increased magnitude of (Shettigar and Hultgren) 1 (Letter to Editor)
 Reply (Bianco) 34
- Testing function soon after acute myocardial infarction (Nyden et al.) 1 (Letter to Editor)
- Therapeutic considerations with infective endocarditis (Wilson et al.) 606
- Therapy antihypertensive new pharmacologic approaches (Stokim Oates and Maffei) 41
 verapamil (Ahmad) 71 (Letter to Editor)
 Reply (Fazzini et al.) 71
- Thermal illness in fun running (Sutton and Bar Or) 74
- Thermosensitivity of cutaneous vessels and Raynaud's disease (Vanhoutte and Janssens) 953 (Annot)
- Thomas Young M.D. (1773-1859) (Laird) 1
- Thrombi, ventricular left echocardiographic diagnosis (Come et al.) 523
- Thromboembolism venous, prophylaxis of (Farrell and Duffy) 134 (Letter to Editor)
- Thrombosis central retinal vein in a patient with primary pulmonary hypertension (Berliner et al.) 134 (Letter to Editor)
- deep vein and transvenous temporary pacing (Pardus Kosowsky and Gurewicz) 81
- intraventricular in polythrombosis a cause of intracardiac cardiac failure (Ali et al.) 570
- Thrombus left atrial ball diagnosed by two-dimensional echocardiography (Sunagawa et al.) 89
 evaluation of with computed tomography (Tomoda et al.) 306
- Tissue hyperplasia connective accompanying muscular hypertrophy constituents of the human ventricular myocardium (Moore et al.) 610
- Tocainide a prospective randomized trial of in patients following myocardial infarction (Bartun et al.) 1017
 for drug resistant ventricular arrhythmias efficacy side effects and lidocaine responsiveness for predicting tocainide success (Winkle Mason and Harman) 1031
 for refractory ventricular arrhythmias of myocardial infarction (Haffajee Alpert, and Dalen) 1013
 hemodynamic and antiarrhythmic effects of in patients with acute myocardial infarction (Nyquist et al.) 1003
 and electrophysiologic interactions between antiarrhythmic drugs and beta blockers with special reference to (Ikram) 106
- intravenous and oral, prophylaxis of ventricular tachyarrhythmias with in patients with and recovering from acute myocardial infarction (Rydén et al.) 1006
- oral, treatment of ventricular arrhythmias with (Young et al.) 1041
- safety evaluation of in the American Emergency Life Program (Horn et al.) 1037
- success efficacy side effects and lidocaine responsiveness for predicting tocainide for drug resistant ventricular arrhythmias (Winkle Mason and Harman) 1031
- therapy chronic maintenance in patients with recurrent sustained ventricular tachycardia refractory to conventional antiarrhythmic agents open clinical studies at a referral center (Malonev Nassen and McCollan) 1023
- for refractory ventricular arrhythmias (Rodin et al.) 15
- Tomography computed evaluation of left atrial thrombus with (Tomoda et al.) 306
- Torsades de pointes as a manifestation of mexiletine toxicity (Cocco et al.) 678
- Toxic polyneuritis and toxic hepatitis related to long term perhexiline maleate therapy (Caruzzo et al.) 770
 (Letter to Editor)
 Reply (Muri) 271
- Toxicity mexiletine torsades de pointes as a manifestation of (Cocco et al.) 678
- Tract digestive as a cause of chest pain (Long et al.) 577
- Transesophageal cross-sectional echocardiography (Hassan et al.) 903
- Tran femoral temporary pacing and deep vein thrombosis (Landan Kosowsky and Gurewicz) 81
- Trauma chest blunt in a young woman delayed acute myocardial infarction after (Vlay et al.) 907
- Treadmill exercise stress test errors in predicting functional capacity from a (Hagg et al.) 581 (Annot)
- Treatment for primary pulmonary hypertension (Lokel) 36 (Annot)

Echocardiographic—continued

- diagnosis of left ventricular thrombi (Come et al) 573
 features of a stenotic porcine aortic valve (Alam and Goldstein) 51
 pattern of motion of the aortic root as a correlate of left atrial volume changes (Biamino et al) 191
 study cross-sectional, on persistent left superior vena cava (Hibi et al) 69
- Echocardiography cross sectional spec and subphoid approaches to Ebstein's anomaly using (Kambe et al) 53
 III Analysis of mathematic models for quantifying volume of symmetric and asymmetric left ventricles (Wyatt et al) 871
 transesophageal (Hisanaga et al) 605
 two-dimensional left atrial ball thrombus diagnosed by (Sotogawa et al) 89
- Ectopic activity ventricular during cardiac rehabilitation heart rate levels and (Simons, Lap and Pool) 9
- Effective coronary care and mortality rates (Adge) 408 (Letter to Editor)
 Reply (Hampton) 408
- 14th century cardiopulmonary resuscitation an element of sophistication in the (Bartecchi) 580 (Annot)
- Elastic and rigid forms of constrictive pericarditis on the (Hancock) 917
- Electrocardiographic (ECG) and PGC recordings anomalous (Gurel) 68 (Letter to Editor)
 Reply (Basta) 58
- left ventricular hypertrophy and coronary artery disease clinical hemodynamic and angiographic correlates (Hamby et al) 794
 pathologic correlative study on left axis deviation in hypertensive hearts (Takagi and Okada) 838
 recording dynamic during sexual activity in recent post myocardial infarction and revascularization patients (Paolillo et al) 763 (Letter to Editor)
 Reply (Johnston and Fletcher) 763
- Electrode pacing redundant migration of (Perelman and Shui) 591 (Letter to Editor)
 Reply (Rettig) 591
- Electrophysiologic and hemodynamic interactions between antiarrhythmic drugs and beta blockers with special reference to tocainide (Ikram) 106
 effects of intravenous lidocaine in the Wolff-Parkinson-White syndrome (Barrett et al) 23
- Emergency Use Program American safety evaluation of tocainide in the (Horn et al) 1037
- Encainide a new and potent antiarrhythmic agent (Harrison et al) 1046
- Endocarditis infective therapeutic considerations (Wilson et al) 689
- Endomyocardial fibrosis right ventricular simulating Ebstein's anomaly (Alipour Tarbiat and Nazarian) 89
- Entry of quinidine into cerebrospinal fluid (Ochs et al) 341
- Epilepsy arrhythmogenic an hypothesis (Pritchett, McNamara and Gallagher) 683
- Errors in predicting functional capacity from a treadmill exercise stress test (Ragg et al) 581 (Annot)
 Reply (Schaefer) 944 (Letter to Editor)
- Exmo Lo the poor (Schaefer) 944 (Letter to Editor)
- Exercise and recurrence of myocardial infarction (Shepherd) 404 (Annot)
 hemodynamics and increased magnitude of P terminal for a correlation between (Shettig and Hultgren) 590 (Letter to Editor)
 Reply (DiBianco) 590
- symmetric handgrip cardiovascular disease at rest and during norepinephrine levels in the coronary sinus in patients with (Haneda et al) 465
- pharmacological, isoproterenol, and atropine effects of T wave abnormalities in top ranking athletes (Zepplin et al) 213
- rehabilitation of female patients with coronary heart disease (Oldridge, LaSalle and Jones) 755 (Annot)
 stress test treadmill, errors in predicting functional capacity from a (Ragg et al) 581 (Annot)

- Extracranial to intracranial microvascularization for the treatment of completed ischemic stroke (Greenhalgh et al) 93 (Annot)
- Extrastimuli ventricular repetitive responses to incidence mechanism and significance (Farboudi et al) 59

F

- Fabry's disease the M mode echocardiogram in (Biv et al) 80
- Failure heart congestive of right ventricular (Burch) 262 (Annot)
- Female patients with coronary heart disease exercise rehabilitation of (Oldridge, LaSalle and Jones) 755 (Annot)
- Fever rheumatic in children on (Aryanspur, Khamis) 947 (Letter to Editor)
 Reply (DiScia and Taranta) 943
- Fibrillation atrial with Brugada's sign (Buxton) 411 (Letter to Editor)
- Fibrosis endomyocardial right ventricular simulating Ebstein's anomaly (Alipour Tarbiat and Nazarian) 89
 septal electrocardiographic syndrome of coronary arteriograms and myocardial scintigrams in the (Romanelli et al) 617
- First derivative of the apexcardiogram evaluation of contractile state of the left ventricle from the peak of the (Kolev) 600
- Fluid cerebrospinal entry of quinidine into (Ochs et al) 341
- Flutter and ventricular tachycardia pacing below the ventricular rate in terminating (Cotot et al) 763 (Letter to Editor)
- Fructose diphosphate hemodynamic electrocardiographic and metabolic effects of on acute myocardial ischemia (Markov et al) 637
- Fun running thermal illness in (Sutton and Bar Or) 778
- Function testing soon after acute myocardial infarction (Vanden et al) 590 (Letter to Editor)
- Functional capacity errors in predicting from a treadmill exercise stress test (Ragg et al) 581 (Annot)
 right bundle branch block site of (Lyons) 653

G

- Gastrointestinal bleeding aortic stenosis associated with A survey of 612 patients (Shoenfeld et al) 179
- Giant cell arteritis—a cardiologic blind spot? (How, Strachan and Bewsher) 405 (Annot)
 (cranial) arteritis a clinical review (Huston and Hunder) 99
- Glucose in ultra potassium nitrates beta blockade and hyaluronidase comparison of anti-infarct effects of Part 2 of Myocardial infarct site (Opie) 531
- Grading system Lown shortcomings of for observational and experimental studies in ischemic heart disease (Bigger and Weld) 1081
- Grafts bypass saphenous vein antithrombotic therapy for? (Goodnight, Pantley and Rahumtoola) 587 (Annot)

H

- Heart and coronary arteries clinicopathological study of the in autopsied cases from the community of Hisayama during a 10 year period Part IV QRS waves in the precordial leads (Hiroshi et al) 424
- disease and pregnancy certain principles in the management of (Burch) 75
- coronary alcohol and (Evans, Willett and Hennkens) 584 (Annot)
 and smoking what are we to believe (Seltzer) 275

Introduction

The articles appearing in this issue were presented at the Symposium on Cardiac Arrhythmias: A Decade of Progress—1980 held at Stanford University School of Medicine on May 8, 9 and 10, 1980. The conference provided a 10-year update on the first such symposium held in 1970 at Eltunor, Denmark, and featured many of the same participants. The symposium as well as this publication were made possible by a generous educational grant from Astra Pharmaceutical Products Inc. of Framingham, Massachusetts. These papers relate to new antiarrhythmic drugs and their comparative study and to other devices for managing patients with life-threatening ventricular arrhythmias unresponsive to treatment by drugs. The complete transcript of the symposium will be published later in book form by G. H. Hall & Co., Boston, Massachusetts.

In Section I, Ronfeld, Jewitt, and Lawrie detail comparative data now available on new antiarrhythmic agents currently under investigation in Europe and the United States. While these data are still incomplete for several of the new membrane-active drugs, the summaries are the most comprehensive now available.

Sections II and III outline studies in patients with coronary artery disease with tocainide, an analog of lidocaine with Class I (membrane) activity. The antiarrhythmic hemodynamic and toxicity data for patients with acute myocardial infarction demonstrate that tocainide is effective and safe. Some patients do develop side effects, but discontinuation of treatment is rarely required. Long-term administration of tocainide in patients with arrhythmias resistant to therapy with available agents is reported by Maloney and Winkle in Section III. Horn summarizes safety

data from the compassionate clearance protocol, and Young presents the results of a series of planned protocols to evaluate tocainide's effectiveness.

In Section IV, Harrison, Zipes, Coumel, and Schamroth describe their extensive experience with four other promising new antiarrhythmic agents: encainide, aprindine, amiodarone, and verapamil.

In Section V, the interaction of tocainide with beta blocking agents is discussed by Ikram. Bigger presents convincing evidence that the Lown classification for premature ventricular contractions has many shortcomings and thus is not helpful in studying newer antiarrhythmic agents. Griffin and Mrowka describe early experiences with implantable devices for detecting and electrically terminating arrhythmias.

The 1970s truly represented a decade of progress in arrhythmia research. New and sophisticated methods for detecting arrhythmias have been developed. Pharmacokinetics has become an accepted clinical science and provides us with a more rational means for administering antiarrhythmic agents. Drugs with different mechanisms of action have been introduced for trial and offer the hope of effective and safe prophylaxis and treatment of malignant arrhythmias. Improved electrophysiologic study techniques have provided understanding of arrhythmia mechanisms and supply a means of designing circuitry for detection and electrical termination of arrhythmias.

The 1980s, no doubt, will see substantial additional progress and excitement in this developing field.

Donald C. Harrison, M.D.

Comparative pharmacokinetics of new antiarrhythmic drugs

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The importance of pharmacokinetics to drug therapy is routinely accepted by many clinicians and especially cardiologists today. Certainly the pharmacokinetics of a drug are a consideration when a dosage regimen is being designed for a drug and may even be a factor when a choice in drug therapy is being made. A working knowledge of a drug's pharmacokinetics can be essential in cardiology since the kinetics of the drug may be altered by the patient's disease state or affected by the multiplicity of drugs the patients may be receiving.

The objective of this report is to review the pharmacokinetics of several new antiarrhythmic agents. Unfortunately, there is a paucity of data on some of the new and possibly significant drugs. For the most part, these data have been abstracted from the literature. Certainly in the coming years, as new analytic techniques are developed, much of these data will be modified or viewed as incorrect. The basic principles of pharmacokinetics will not be reviewed here since these have been covered satisfactorily in a recent review on antiarrhythmics.

The pharmacokinetics of the established antiarrhythmics, lidocaine, quinidine, and procainamide, will not be reviewed in detail. Because of their short half-lives, neither of these prototypes has been satisfactory for once or twice daily administration. Therefore, on the basis of half-life alone, a new antiarrhythmic agent could be a therapeutic improvement. Also, in the steady state, each of these three drugs has metabolite levels that could contribute to their overall activity. The presence of an active metabolite certainly

will make the interpretation of clinical blood or plasma samples more difficult. Active metabolites may also increase the interpatient dose response variability. In the future, there will very likely be a number of antiarrhythmics for the clinician to select from. The predictability and convenience of a dosage regimen may then be an important consideration in selecting an appropriate drug.

Tocainide

Tocainide and lidocaine have similar pharmacologic and electrophysiologic properties. Tocainide is less potent than lidocaine in direct cardiac effects and in central nervous system (CNS) effects. Tocainide is a primary amine, in contrast to the tertiary amine lidocaine, and consequently the free base is 20 times less lipophilic in an octanol-water system.

Aside from potency, the major difference between lidocaine and tocainide resides in their pharmacokinetics. Tocainide has a 11 to 13-hour half-life in healthy volunteers. In patients, the mean half-life was also 13 hours, although the variability was greater than with the volunteers.¹ The plasma protein binding of tocainide was constant over the therapeutic range with approximately 50% bound. The renal clearance of free drug was approximately equivalent to the expected glomerular filtration rate. Typically, 40% of an oral dose is excreted unchanged in the urine and 25% is excreted as a glucuronide conjugate of *N*-carboxytocainide. Total body clearance in both patients and volunteers was 110 to 140 ml/min.²

Plasma levels above 5 µg/ml are reported to be effective in reducing the frequency of premature ventricular beats. Plasma concentrations above 5.0 and 8.3 µg/ml resulted, on the average, in 70% and 90% reductions in premature beats. Other

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1 1/2-1-coronary

- see myocardial Part I Basic considerations (Opie) 3:5
 Part 2 Comparison of anti-infarct effects of beta blockade, glucose-insulin-potassium, nitrates, and hialuronidase (Opie) 531
- Infarct myocardium cardiac lymph and lymphatics in normal and (Salvy et al.) 3:3
- Infarction, myocardial, acute early diagnosis of pericarditis in (Sawaya Mujas and Arsenian) 144
- delayed, after blunt chest trauma in a young woman (Wey et al.) 90
- effects of ouabain on the electrophysiological properties of subendocardial Purkinje fibers surviving in regions of (Brennan and Bonn) 201
- function testing soon after (Lyden et al.) 300 (Letter to Editor)
- hemodynamic and antiarrhythmic effects of tocinamide in patients with (Vivquist et al.) 1000
- hospitalized patients over age 70 (Laiting and Silverman) 311
- infarct expansion the "second event" after (Silverman and Huchana) 230
- platelet controlled study of prophylaxis of ventricular arrhythmias in (Campbell) 935
- prophylaxis of ventricular tachyarrhythmias with intravenous and oral tocinamide in patients with and recovering from (Ryden et al.) 1000
- exercise and recurrence of (Shepherd) 404 (Annot.)
- in hypertensive subjects, limited pressure control to optimum levels may reduce the rate of (Stewart) 407 (Annot.)
- of the Q wave and (Burch) 757 (Annot.)
- prospective randomized trial of tocinamide in patients followed (Bastian et al.) 1017
- serum myoglobin as a sensitive index of (Grenader Heidar and Palant) 948 (Letter to Editor)
- Reply (Tommaso) 949
- tocinamide for refractory ventricular arrhythmias of (Haf faje Alpert, and Dalen) 1013
- post myocardial, and revascularization patients, recent dynamic electrocardiographic recording during sexual activity in (Paolillo et al.) 63 (Letter to Editor)
- Reply (Johnston and Fletcher) 763
- infarctous hazards of mouth-to-mouth resuscitation (Achoing) 708 (Annot.)
- infective endocarditis therapeutic considerations (Wilson et al.) 688
- isotropic act on ef digitalis and isoproterenol in younger and older individuals comparison of the (Cokkino et al.) 807
- insulin infusion, continuous subcutaneous a new approach to improved metabolic control in diabetics (Pickup) 417
- intracardiac phonocardiography in experimental left ventricular cavity obliteration potential clinical applicability for the distinction of obliterating left ventricle from hypertrophic obstructive cardiomyopathy (Sabbah, Marzilli, and Stein) 77
- intracavitary stimulation and left stellatectomy Romano-Ward syndrome treated by (Chaudron and Lebaeq) 131 (Annot.)
- intracranial to extracranial microvascularization for the treatment of completed ischemic stroke (Greenhalgh et al.) 937 (Annot.)
- intractable cardiac failure intraventricular thrombosis in polycythemia vera a cause of (Ah et al.) 520
- intravenous lidocaine in the Wolff Parkinson White syndrome electrophysiologic effects of (Barrett et al.) 23
- verapamil, the clinical use of (Schamroth) 1070
- intraventricular thrombosis in polycythemia vera a cause of intractable cardiac failure (Ah et al.) 520
- Introduction to Supplement (Harrison) 977
- ischemia myocardial, acute hemodynamic electrocardiographic and metabolic effects of fructose diphosphate on (Markov et al.) 639

Ischemia myocardial-continued

- non thrombotic chronic use of aspirin versus indomethacin during effects on survival (Moschos et al.) 647
- Ischemic cardiomyopathy a clinicopathologic study of four teen patients (Schuster and Bulkley) 507
- heart disease shortcomings of the Lown grading system for observational and experimental studies in (Bigger and Weld) 1081
- models, antiarrhythmic in effects of (Bauman Curtis, and Covinsky) 947 (Letter to Editor)
- myocardium recovery time course of ventricular vulnerability after coronary reperfusion in relation to mitochondrial function in (Sugiyama et al.) 829
- stroke completed extracranial to intracranial microvascularization for the treatment of (Greenhalgh et al.) 937 (Annot.)
- Isometric handgrip exercise cardiovascular disease at rest and during norepinephrine levels in the coronary sinus in patients with (Haneda et al.) 465
- Isoproterenol and digitalis in younger and older individuals, comparison of the inotropic action of (Cokkino et al.) 802
- atropine and physical exercise effects of T wave abnormalities in top-ranking athletes (Zeppilli et al.) 213
- Isovolumic relaxation period in man (Lewis et al.) 490

L

- Langendorff perfused rabbit heart isolated cardiac damage caused by direct application of defibrillator shocks to (Koning Veefkind and Schneider) 473
- Leaflet(s) prolapse mitral, myocardial mysteries surrounding (Malcolm) 260 (Annot.)
- valve pulmonary rudimentary. This anomaly with a clinical hemodynamic angiographic and pathologic study (Kaul, Arora, and Rami) 673
- Left atrial ball thrombus diagnosed by two-dimensional echocardiography (Sunagawa et al.) 89
- axis deviation in hypertensive hearts, an electrocardiographic pathologic correlative study on (Takagi and Okada) 833
- to-right shunt, use of the echocardiogram in delineating the location of a congenital heart disease with trisomy 13 (Cabin Lester and Roberts) 563
- ventricle(s) contractile state of the from the peak of the first derivative of the apexcardiogram evaluation of (Kolev) 600
- symmetric and asymmetric analysis of mathematic models for quantifying volume of Cross-sectional echocardiography III (Wyatt et al.) 871
- ventricular free wall and septum ratios of in IHSS and HCM (Shakib, Reyhan, and Nazarian) 66 (Letter to Editor)
- hypertrophy versus aneurysm? (Burns, Culham and Duncan) 67 (Letter to Editor)
- Reply (Singh) 78
- thrombi, echocardiographic diagnosis of (Come et al.) 523
- Libranans, medical, and bibliographies of (Bury and Jones) 591 (Letter to Editor)
- Reply (Burch) 591
- Lidocaine intravenous, in the Wolff Parkinson White syndrome electrophysiologic effects of (Barrett et al.) 23
- responsiveness efficacy and side effects for predicting tocinamide success tocinamide for drug resistant ventricular arrhythmias (Winkle Mason and Harrison) 1031
- Life threatening arrhythmias neural mechanisms in (Mal hani, Schwartz, and Zanchetti) 705
- Limited pressure control to "optimum" levels may reduce the rate of myocardial infarction in hypertensive subjects (Stewart) 402 (Annot.)

workers reported a 75% reduction in ventricular premature beats when the mean peak blood level was 103 $\mu\text{g/ml}$.

There are measurable levels of two metabolites in plasma: the previously mentioned glucuronide and lactoylhydride which is the product of oxidative deamination.³ Based on animal pharmacologic data it appears that the metabolites do not contribute to the efficacy or CNS side effects of tocainide.

Mexiletine

Mexiletine is a primary amine structurally similar to tocainide. Mexiletine has an ether linkage between the benzene ring and alkyl chain whereas tocainide has an amide linkage. Because of this structural difference mexiletine has a higher pK_a and much larger octanol/water partition coefficient.

The half life of mexiletine was 9 to 12 hours in volunteers. In patients mean half lives of 12 and 13 hours were reported as well as a mean of 16.7 hours for patients with acute myocardial infarction. The volume of distribution was large and reported as 6.6 and 8.1 L/kg in patients and 500 to 660 L in volunteers. Total body clearance was also large at 6.5 and 7.1 ml/min/kg. There are conflicting reports on the importance of renal excretion. At a normal and unadjusted urinary pH 8% to 20% was excreted unchanged. However at a urine pH of 5 renal excretion increased to 40% to 60% and renal clearance increased by a factor of 3 to 4.¹ However the effect of normal physiologic variation in pH remains controversial. At least in acute myocardial infarction (AMI) patients there were large intersubject variations in plasma levels with trough levels varying by an order of magnitude.¹ The oral absorption and plasma levels were significantly reduced when mexiletine was concomitantly administered with morphine or diamorphine. This negative effect on absorption is probably not unique for mexiletine and these investigators suggested that this may also occur with other drugs and antiarrhythmics.

Effective plasma levels are reported to be 0.75 to 2.0 $\mu\text{g/ml}$. The incidence of side effects including nausea, tremor and hypotension increased at plasma levels above 2.0 $\mu\text{g/ml}$. Mexiletine has been used both intravenously and orally and in the early stages of myocardial infarction. Assuming it is effective there is an advantage to using

the same drug for initial intravenous administration and maintenance oral administration. Unfortunately because of the narrow therapeutic range the intravenous dosing schedule is complex.

Lorcanide

Lorcanide is a new antiarrhythmic in which there have only been preliminary reports on its electrophysiologic and antiarrhythmic properties. However the pharmacokinetics of this new antiarrhythmic have been reported in detail.

The terminal half life in patients with chronic ventricular premature contractions was reported to be 7.7 hours by two separate groups of investigators.¹ There were dramatic differences among subjects with half lives varying from 2.6 to 15.2 hours. The volume of distribution was very large at 8 to 10 L/kg. The plasma and blood clearances were 1,000 and 1,500 ml/min respectively. Only a few percent of the dose was excreted unchanged in the urine. Since the clearance is approximately equivalent to liver blood flow we would expect a large first pass effect if metabolism occurs in the liver. Based on a single 100 mg oral dose this assumption would appear correct since only 4% of the dose was bioavailable. However the bioavailability increased to 30% to 60% with a 200 mg dose and increased to 45% to 200% with multiple 100 mg doses. Apparently metabolic saturation occurs with oral administration. There are probably two factors contributing to this: the concentration presented to the liver can be much higher after an oral dose than after an intravenous dose and at least with multiple dosing there may be product or metabolite inhibition. This dose-dependent bioavailability may also occur with drugs such as propranolol and alprenolol which also have high hepatic clearances.

The primary metabolite in plasma appears to be a N -dealkylated lorcanide or norlorcanide. At steady state the norlorcanide/lorcanide ratio is approximately 3 with oral administration and 1 with intravenous administration. The activity of both compounds measured either as reduction in ventricular premature contractions (VPCs) or QRS widening was similar. An effective antiarrhythmic dose appears to be around 100 mg tid which resulted in steady state plasma levels of 300 and 900 ng/ml for lorcanide and norlorcanide respectively.

Lipophilicity and cardiospecificity in beta blockers: the clinical importance of (Cruckshank) 160
 Lo—the poor Eskimo? (Schaefer) 944 (Letter to Editor)
 Reply (Oster) 945
 Long term benefit of dobutamine in patients with congestive cardiomyopathy (Unverferth et al) 622
 Low n grading system: shortcomings for observational and experimental studies in ischemic heart disease (Bigger and Weld) 1081
 Lung disease: hypoxic management of secondary polycythemia with (York et al) 267 (Annot)
 Lymph and lymphatics cardiac in normal and infarcted myocardium (Szlavy et al) 323
 Lymphatics and lymph cardiac in normal and infarcted myocardium (Szlavy et al) 323

M

Malignant granular cell myoblastoma with metastatic cardiac involvement: case report and echocardiogram (Kubac et al) 227
 Management of heart disease and pregnancy: certain principles in the (Burch) 775
 Mapmaker: cardiologist the responsibility of the (Nixon) 139
 Medical clinic and the cost of unnecessary tests: the importance of the history in the (Sandier) 928 (Annot)
 Bibliography and bibliographies of (Bury and Jones) 591 (Letter to Editor)
 Reply (Burch) 591
 Metabolic control in diabetes: new approach to continuous subcutaneous insulin infusion (Pickup) 417
 Metastatic cardiac involvement with malignant granular cell myoblastoma: case report and echocardiogram (Kubac et al) 227
 Mexiletine and amiodarone treatment combined for refractory recurrent ventricular tachycardia (Waleffe et al) 88
 Multiple de pointes as a manifestation of (Cocco et al) 85
 Myocardial calcification extracranial to intracranial for the treatment of completed ischemic stroke (Greenhill et al) 33 (Annot)
 Migration of redundant pacing electrode (Perelman and Hira) 91 (Letter to Editor)
 Reply (Hetting) 91
 Mitochondrial function in ischemic myocardium: recovery time course of ventricular vulnerability after coronary reperfusion in relation to (Sugawara et al) 989
 Mitral leaflet prolapse: myocardial myxomas surrounding (Malcolm) 76 (Annot)
 Prosthetic dehiscence and paraprosthetic regurgitation (Ikahama) 940 (Letter to Editor)
 Reply (Hun et al) 940
 Mitral rheumatism: cross sectional echocardiographic analysis (Naito et al) 34
 Atrial and arrhythmias of the (Burch) 383 (Annot)
 Disease: obstructive relationship of pulmonary artery wedge pressure to the posterior aortic wall echocardiogram in patients free of (Wasserman Meyer and Roes) 88
 Premature death and sudden death (Anderson) 942 (Letter to Editor)
 Reply (Latham and Bingham) 942
 In aneurysmal rupture: (Venkatesh et al) 97
 Site of origin of ventricular premature beats in patients with (Latham and Bingham) 942
 Sudden death (Murray) 409 (Letter to Editor)
 Reply (Murray) 409
 Sudden death: myocardial and (Hoss and Straube) 41 (Letter to Editor)
 Reply (Hoss) 41
 Mode echocardiogram: Fat and the (Biss et al) 407

Mortality rates and effective coronary care (Adgey) 1000 (Letter to Editor)
 Reply (Hampton) 408
 Mouth-to-mouth resuscitation: infectious hazards of (Achoff) 769 (Annot)
 Murmurs: papillary muscle dysfunction of (Burch) 13 (Annot)
 Muscular hypertrophy: connective tissue hyperplasia accompanying constituents of the human ventricular myocardium (Moore et al) 610
 Myoblastoma: malignant granular cell, with metastatic cardiac involvement: case report and echocardiogram (Kubac et al) 227
 Myocardial bridges: relief of angina by percutaneous muscle resection of (Bertru et al) 223
 Disease: primary diabetes mellitus and small vessel disease (Zonerach Silverman and Zonerach) 34 (Annot)
 Infarct size: Part I: Basic considerations (Opie) 33
 Part 2: Comparison of anti-infarct effects of beta-blockade, glucose, insulin, potassium, nitrates, and hyaluronidase (Opie) 531
 Infarction: acute delayed after blunt chest trauma in a young woman (Vlay et al) 907
 Early diagnosis of pericarditis in (Sawaya Mujan and Armenian) 141
 Effects of ouabain on the electrophysiological properties of subendocardial Purkinje fibers surviving in regions of (Brennan and Bonn) 701
 Function: testing soon after (Vjden et al) 590 (Letter to Editor)
 Hemodynamic and antiarrhythmic effects of tocamide in patients with (Nyquist et al) 1000
 In hospitalized patients over age 70 (Lattin and Silverman) 311
 Infarct expansion: the second event after (Sihemian and Huchima) 230
 Placebo controlled study of prophylaxis of ventricular arrhythmias in (Campbell) 69
 Prophylaxis of ventricular tachyarrhythmias with intravenous and oral tocamide in patients with and recovering from (Hjden et al) 1000
 Exercise and recurrence of (Shephard) 404 (Annot)
 In hypertensive subjects: limited pressure control to optimum? levels may reduce the rate of (Stewart) 407 (Annot)
 Of the Q wave and (Burch) 77 (Annot)
 Prospective randomized trial of tocamide in patients following (Bastian et al) 101
 Serum myoglobin as a sensitive index of (Crenander Heider and Ialant) 945 (Letter to Editor)
 Reply (Tormmaso) 949
 Tocamide for refractory ventricular arrhythmias of (Hilf) (Jaez Albert and Dalen) 1013
 Ischemia: acute hemodynamic electrocardiographic and metabolic effects of fructose diphosphate on (Makov et al) 639
 Non thrombotic chronic use of aspirin versus indomethacin during effects on survival (Moncho et al) 647
 Myxomas surrounding mitral leaflet prolapse (Malcolm) 76 (Annot)
 Acutograms and coronary arteriograms in the electrocardiographic syndrome of septal fibrosis (Homans et al) 17
 Myocarditis: cytomegalovirus (Wink and Schmitz) 67
 Myocardium: infarcted cardiac lymph and lymphatics in normal and (Szlavy et al) 323
 Ischemic: recovery time course of ventricular vulnerability after coronary reperfusion in relation to mitochondrial function in (Sugawara et al) 989
 Rupture of and mitral valve replacement (Roes and Straube) 947 (Letter to Editor)
 Reply (Cobles) 947
 Ventricular: human constituent of the connective tissue hyperplasia accompanying muscular hypertrophy (Moore et al) 610

Aprindine

Aprindine is a Class I antiarrhythmic agent and local anesthetic. It has electrophysiologic properties similar to lidocaine but exhibits greater potency. In two separate studies with volunteers the average half life was 22 hours with a range of 12 to 66 hours.²¹ However in patients average half lives of 43 and 50 hours with ranges of 20 to 110 hours were found.⁴ Analysis of the data from one volunteer study, in which both cold and radiolabeled drugs were administered implicated a 70% to 80% bioavailability.⁴ This apparently was due to first pass metabolism since the total radioactivity in the plasma was identical for both oral and intravenous doses. The total body clearance in volunteers was approximately 170 ml/min or 2.5 ml/min/kg. In patients it appears to be substantially lower possibly around 70 ml/min.

Plasma levels effective in suppressing supraventricular or ventricular arrhythmias were generally from 1 to 2 µg/ml. Minor side effects most frequently dizziness occurred in the 2 to 3 µg/ml range. Primary metabolites reported have been hydroxylation on the phenyl and indanyl rings and desethylaprinidine.⁴

Disopyramide NORPACE

Disopyramide is an established antiarrhythmic with electrophysiologic properties similar to quinidine. Half lives in volunteers are generally reported to be 7.0 to 8.0 hours. However these half lives may not be real or meaningful since the plasma protein binding of disopyramide changes dramatically with concentration and even within the therapeutic range.

It has been reported that free fraction in plasma increased by 4% to 100% as total concentration increased over the therapeutic range. Because of the nonlinearity in protein binding total plasma concentration and area under the plasma curve are not proportional to dose. However the concentration of nonprotein bound drug in plasma is proportional to dose. It appears that clearance is only dependent on free drug and consequently changes in protein binding do not affect the free concentration. The half life of the free drug in plasma has been reported to be 3.5 to 4.5 h.²² Since the clearance of free drug is constant with dose and concentration we would not expect changes in binding to be of any consequence in plasma

colytic activity. However, this makes interpretation and dosage adjustment based on total plasma concentration very difficult. The determination of free concentration is not a routine procedure in most laboratories. The therapeutic range for disopyramide in terms of total concentration is reportedly 2 to 7 µg/ml.¹

Disopyramide phosphate (Norpace) had an 80% to 90%²³⁻²⁵ bioavailability when oral versus intravenous plasma levels were used as a criterion and 90% when urinary excretion was used.²⁶ Because of its short half life it is generally administered at 6 or 8 hour intervals. However a sustained release product has been developed which allows for a 12 hour dosage schedule.²⁴

Approximately 50% to 60% of an intravenous or oral dose can be recovered as unchanged drug in the urine.¹⁻⁴ The major metabolite appears to be *N*-disopropylidisopyramide which accounts for another 25% of the dose in urine. At steady state the plasma levels of the metabolite were approximately one third of the parent compound.

Verapamil - ISOPTINE

Verapamil has been recognized as an antiarrhythmic agent for many years. Even before specific analytic methods were developed it was recognized that the drug was probably rapidly metabolized since the effective oral dose was 10 to 15 times the required intravenous dose.

Although there has been extensive work on the pharmacology and electrophysiology of this compound there is a paucity of data on its pharmacokinetics. The only complete report indicates that it has a half life of 3 to 4 hours following a 10 mg intravenous dose. The total body plasma clearance in three subjects 59 to 69 years of age varied from 730 to 1120 ml/min (mean 106 ml/min/kg). Only 5% of the dose was excreted unchanged in the urine. Although it was not done in a crossover fashion the apparent bioavailability was only 10% to 20% following an 80 mg oral dose. This low availability was apparently due to a large first pass effect since based on radioactivity absorption was complete. The volume of distribution was large at 60 l/kg and the plasma protein binding was 90%.

As with other drugs with large hepatic clearances such as lorazepam and propranolol we would expect a large inter-subject variability in plasma levels following oral administration.

Table I Pharmacokinetic parameters of antiarrhythmics in man

| Antiarrhythmics | $T_{1/2}$ (hr) | V_d (L/kg) | Clearance (ml/min/kg) | Bioavailability (%) | Renal excretion (%) | Reference |
|-----------------|-------------------|-----------------|--------------------------|------------------------|------------------------|-----------|
| Quinidine | 6.3 | 2.5 | 4.7 | 70 | 20 | 44 |
| Procainamide | 3.0 | 2.9 | 9.0 | 75 | 60 | 45 |
| Lidocaine | 1.8 | 1.6 | 10.0 | 30 | 5 | 46 |
| Tocainide | 13.0 | 2.8 | 2.4 | 95 | 40 | See text |
| Mexiletine | 13.0 | 6.6 | 6.6 | 85 | 10 | See text |
| Aprindine | 50.0 | 4.0 | 1.0 | ■ | ■ | See text |
| Lorcanide | 7.7 | 7.9 | 16.1 | ~200 | 2 | See text |
| Verapamil | 3.0 | 5.9 | 12.6 | 12 | 2 | See text |
| Disopyramide | | | | | | |
| Total | 7.0 | 0.5 | 0.9 | 85 | 55 | See text |
| Free | 4.0 | | | | | |
| Bretylum | 7.8 | 1.3 | 19.1 | 25 | 77 | 41 |
| Flecainide | 14.0 | | | 95 | | 42 |

 $T_{1/2}$ = elimination half life V_d = apparent volume of distribution ($V_{d\beta}$ or $V_{d\alpha}$)

There are several metabolites with the *N* de methylated compound apparently the major metabolite in plasma. At steady state this metabolite (norverapamil) and verapamil have approximately equivalent plasma levels. It has been suggested that the therapeutic plasma levels are in the range of 100 to 400 ng/ml. All of the metabolites are less potent than verapamil. Norverapamil had the greatest potency with a 46 less vasodilating potency than verapamil.

Summary

Table I lists pharmacokinetic parameters for eight of the drugs discussed as well as for quinidine, procainamide and lidocaine. Data for two of the new agents, bretylum and flecainide, were not discussed in the text. If possible, these values are from patients. Obviously the individual values, especially those in the critically ill patients, may differ considerably from the mean values listed. Also with a drug such as lidocaine, there is a growing amount of evidence suggesting that clearance and the elimination rate constant decrease for patients receiving infusions longer than 24 hours.

As stated earlier, the three older drugs, quinidine, procainamide and lidocaine, all have less than ideal pharmacokinetic properties for easily maintaining constant blood levels. Of course, one solution to this has been to develop sustained release dosage forms. Of the new drugs listed, tocainide, mexiletine, aprindine and flecainide all have high bioavailability and a half life that may

allow for twice daily administration. The feasibility of twice daily administration depends on the therapeutic range and the difference between the maximum and minimum concentrations. For a half life of 12 to 14 hours, we could expect a 1.5 to 2.0 ratio in maximum to minimum concentrations.

With disopyramide, a half life is listed for both free and total drug. Also, volume of distribution and clearance are given for total disopyramide in order to be consistent and comparable with the other drugs listed. As discussed earlier, the value for free disopyramide is the most meaningful.

With both verapamil and lorcanide, there is a potential for a large first pass metabolism. However, in the case of lorcanide, apparent metabolic saturation results in an apparent 100% bioavailability.

These pharmacokinetic data may or may not be used in a clinical setting. Very possibly, though, a blood or plasma sample will be sent to the laboratory for drug analysis. When obtaining a drug level, questions to ask yourself or the laboratory might be: (1) Is the value reliable, was the assay method specific, and could the blood sampling tube or technique lead to a false value? (2) How can these data, along with other clinical and symptomatic data, be used to stabilize or improve therapy?

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- Phentolamine and IHSS (Moreyra and Alday) 134 (Letter to Editor)
- Reply (Kerin) 134
- Pheochromocytoma clinically unsuspected fatal complication of perioperative hypertensive crisis and hemorrhagic diathesis (Lee Olney and Spittell) 716
- Phonocardiographic and auscultatory manifestations case report and review of in right ventricular myxoma (Hada et al.) 871
- and electrocardiographic recordings anomalous (Gurel) 63 (Letter to Editor)
- Reply (Basta) 68
- Phonocardiography intracardiac in experimental left ventricular cavity obliteration potential clinical applicability for the distinction of obliterating left ventricle from hypertrophic obstructive cardiomyopathy (Sabbah Marzilli, and Stein) 77
- Placebo controlled study of prophylaxis of ventricular arrhythmias in acute myocardial infarction (Campbell) 993
- Pneumonia, possible association of with amiodarone therapy (Rotmensch et al.) 412 (Letter to Editor)
- Polycthemia secondary with hypoxic lung disease management of (York et al.) 267 (Annot)
- versus intraventricular thrombosis in a cause of intractable cardiac failure (Ali et al.) 520
- Polyneuritis toxic and toxic hepatitis related to long term perhexiline maleate therapy (Caruzzo et al.) 270 (Letter to Editor)
- Reply (Mir) 271
- Poor Ekumo Lo the (Schaefer) 944 (Letter to Editor)
- Reply (Osteri) 945
- Force aortic valve stenotic echocardiographic features of (Alam and Goldstein) 517
- Possible association of pneumonia with amiodarone therapy (Rotmensch et al.) 412 (Letter to Editor)
- Post myocardial infarction and revascularization patients recent dynamic electrocardiographic recording during sexual activity in (Paolillo et al.) 763 (Letter to Editor)
- Reply (Johnson and Fletcher) 763
- Precordial leads Q waves in the Part IV of Clinicopathological study of the heart and coronary arteries of autopsied cases from the community of Hisayama during a 10-year period (Hiyoshi et al.) 424
- Pregnancy and heart disease certain principles in the management of (Burch) 35
- Risks of anticoagulation during (Paul, Hall, and Wilson) 61 (Annot)
- Premature beats suppression ventricular relation of to serum quinidine concentration determined by a new and specific assay (Carliner et al.) 493
- ventricular site of origin in patients with mitral valve prosthesis (Lichtenstein) 400
- Intensive control limited to optimum levels may reduce the rate of myocardial infarction in hypertensive subjects (Stewart) 402 (Annot)
- Pulse contour analysis in determining the effect of vasodilator drugs on vascular hemodynamic impedance characteristics in dogs (Zobel et al.) 81
- Primary myocardial disease diabetes mellitus and small vessel disease (Zonerach Silverman and Zonerach) 41 (Annot)
- pulmonary hypertension central retinal vein thrombosis in a patient with (Berliner et al.) 134 (Letter to Editor)
- new approaches to therapy (Rubin and Peter) 37 (Annot)
- treatment for (Hinke) 37 (Annot)
- Prolapse mitral leaflet myocardial metastases surrounding (Valcovich) 77 (Annot)
- Idiopathic and sudden death (Anderson) 431 (Letter to Editor)
- Reply (Leatham and Engel) 431
- Site of origin of ventricular premature beats (Lichtenstein) 402

Prolapse—continued

- syndrome mitral valve (Mavric) 409 (Letter to Editor)
- Prophylaxis of venous thromboembolism (Farrell and D'Amico) 134 (Letter to Editor)
- of ventricular arrhythmias in acute myocardial infarction, placebo controlled study of (Campbell) 993
- tachyarrhythmias with intravenous and oral tocaine in patients with and recovering from acute myocardial infarction (Ryden et al.) 1006
- Prospective randomized trial of tocaine in patients following myocardial infarction (Bastian et al.) 1017
- Prosthetic dehiscence mitral and paraprosthesis regurgitation (Ikabeimo) 940 (Letter to Editor)
- Reply (Chun et al.) 940
- "Pseudo-tumor" of the right ventricular outflow tract and congenital pulmonary valve regurgitation a case report (Lutz et al.) 349
- Psychosis, aprindine (Jacobs and Pores) 347
- Psychosocial and behavioral influences in the pathogenesis of acquired cardiovascular disease (Buell and Elliott) 723
- Pulmonary artery wedge pressure to the posterior aortic wall echocardiogram in patients free of obstructive mitral valve disease relationship of (Wasserman, Meyer and Ross) 500
- hypertension primary new approaches to therapy (Rubin and Peter) 37 (Annot)
- treatment for (Hinke) 37 (Annot)
- valve leaflets rudimentary Uhl's anomaly with a clinical, hemodynamic angiographic and pathologic study (Kaul Arora and Rani) 673
- regurgitation congenital pseudo-tumor of the right ventricular outflow tract and a case report (Lutz et al.) 349
- Purkinje fibers, subendocardial, electrophysiological properties of effects of ouabain on the surviving regions of acute myocardial infarction (Brennan and Bonn) 201

Q

- Q wave and myocardial infarction of the (Burch) 35 (Annot)
- Q waves in the precordial leads Part IV of Clinicopathological study of the heart and coronary arteries of autopsied cases from the community of Hisayama during a 10-year period (Hiyoshi et al.) 424
- Quinidine concentration serum determined by a new and specific assay relation of ventricular pre-excitation beat suppression to (Carliner et al.) 493
- into cerebrospinal fluid, entry of (Ochs et al.) 341

R

- Ratios of septum and LV free wall in IHSS and HCM (Shakiba, Reyhani, and Nazarian) 66 (Letter to Editor)
- Raynaud's disease and thermosensitivity of cutaneous vessels (Vanhouette and Janssens) 263 (Annot)
- Recordings, anomalous ECG and PEG (Gurel) 63 (Letter to Editor)
- Reply (Basta) 68
- Recovery time course of ventricular vulnerability after coronary reperfusion in relation to mitochondrial action in ischemic myocardium (Sugawara et al.) 829
- Recurrence of myocardial infarction with exercise (Shepherd) 404 (Annot)
- Redundant pacing electrode migration of (Fertman and Shui) 591 (Letter to Editor)
- Reply (Hietala) 591
- Refractory ventricular arrhythmias of myocardial infarction, tocaine for (Haffajee, Alpert, and Dalen) 1017
- tocaine therapy for (Hofen et al.) 15

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Apex and subxiphoid approaches to Ebstein's anomaly using cross-sectional echocardiography

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The diagnosis of Ebstein's anomaly is in typical cases easily suspected from physical findings together with electrocardiography and x-ray examination. In milder forms of the anomaly, however, the diagnosis may be difficult without additional invasive techniques such as angiocardiography.¹ The lesion shows considerable variation in the pathologic anatomy of the malformation and its clinical manifestations.² Since its advent, M-mode echocardiography has served as a useful tool for the diagnosis of Ebstein's anomaly,³⁻⁶ although it is not suitable for the spatial orientation of cardiac structures.

Cross-sectional echocardiography has also provided various clinical information on cardiac anatomy and movements. Recently, apex cross-sectional echocardiography has been introduced to display four cardiac chambers side by side^{7,8} and a subxiphoid approach has been added to conventional M-mode⁹ or cross-sectional echocardiography.¹⁰

The aim of this study is to describe the abnormalities of the tricuspid valve in Ebstein's anomaly

and the chordae tendineae in the right side of the heart using apex and subxiphoid cross-sectional echocardiography.

Materials and methods

Cross-sectional echocardiography was performed on 11 patients with Ebstein's anomaly, isolated or associated with other heart diseases as shown in Table I. They ranged in age from two to 43 years. Five patients were male and the remainder were female. The diagnosis was confirmed by right heart catheterization and angiocardiography in 10 patients and the remaining one was diagnosed by clinical findings and noninvasive diagnostic techniques including echocardiography. One patient underwent cardiac surgery. Two out of the 11 patients showed slight to moderate cyanosis. For the control, 10 patients with atrial septal defect of secundum type were similarly examined in addition to 10 normal subjects.

Cross-sectional echocardiograms were obtained by a commercially available Sonolayergraph of Toshiba SSH 11A.¹¹ This instrument was characterized by its electronic sector scanning system with a wide angle (78 degrees) and 32 element phased array. Its resonant frequency was 2.4 MHz. The scanning speed was 30 cross sections per second and one frame was composed of 112 scanning lines. Furthermore, it was possible to simultaneously record dual beam M-mode echocardiograms by sampling from the cross-sectional

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Table I Displacement of the septal tricuspid leaflet*

| Case no | Name | Sex | Age | Cardiac diagnosis | Displacement of STL (cm) |
|---------|------|-----|-----|------------------------------|--------------------------|
| 1 | H. S | m | 35 | Ebstein's anomaly | 3.2 |
| 2 | T. I | m | 29 | Ebstein's anomaly | 2.0 |
| 3 | F. A | m | 5 | Ebstein's anomaly + PFO | 2.2 |
| 4 | M. T | f | 5 | Ebstein's anomaly + ASD | N.A. |
| 5 | Y. N | f | 2 | Ebstein's anomaly + PFO | 1.6 |
| 6 | T. T | f | 20 | Ebstein's anomaly + PS + ASD | N.A. |
| 7 | K. N | f | 4 | Ebstein's anomaly | 1.4 |
| 8 | J. N | m | 38 | Ebstein's anomaly | 2.4 |
| 9 | A. L | f | 21 | Ebstein's anomaly + PFO | 2.2 |
| 10 | M. S | m | 22 | Ebstein's anomaly | N.A. |
| 11 | R. W | f | 43 | Ebstein's anomaly | 1.8 |

In eight of the 11 patients it was measured in the four-chamber view from the same plane as the anterior mitral leaflet to the root of the septal tricuspid leaflet in end-diastole, using 8 mm cinematography

Abbreviations m = male f = female PFO = patent foramen ovale ASD = atrial septal defect PS = pulmonic stenosis STL = septal tricuspid leaflet N.A. = not available

images. The effective diagnostic depth was 16 cm.

The two dimensional images were obtained in the supine position by directing the cross sectional planes through the cardiac apex and subxiphoid area.

Fig 1 shows the position of the transducer and the direction of the ultrasonic beam. An apical four chamber view was obtained by orienting the transducer from the cardiac apex in the direction A.

This cross section readily provided a four chamber view so as to permit visualization of the interventricular septum connected with the interatrial septum in the middle of the images with both ventricles and atria side by side.

An apical three chamber view was recorded by orienting the transducer in the direction of B which was nearly perpendicular to the cross sectional plane A for the apical four chamber view. This cross section provided a three chamber view of the right side of the heart namely the atrialized and functional right ventricles and the right atrium eliminating the left sided heart chambers.

Furthermore a subxiphoid cross section was obtained by placing the transducer horizontally below the xiphoid process C and occasionally along the left costal margin D to visualize the wider area encompassing the right ventricular cavity to the left sided heart.

Results

Our data were divided into two major categories: the first was the assessment of the down-

ward displacement of the septal tricuspid leaflet in a four chamber view through the cardiac apex and the second was the subxiphoid approach to the evaluation of the subvalvular apparatus such as the chordae tendineae inserting into the tricuspid valve.

1 Apex cross section

a Four chamber view. An apical four chamber view was obtained in all the patients. Fig 2 shows a four chamber view by apex cross section in a 35 year old male (H. S.) with Ebstein's anomaly. The septal tricuspid leaflet (STL) is displaced downward into the right ventricle resulting in the formation of the atrialized right ventricle (ATRV) and functional right ventricle (FRV). The anterior tricuspid leaflet (ATL) is elongated but not displaced from the tricuspid valve ring. Fig 3 shows another example of the four chamber view in a 21 year-old female patient with Ebstein's anomaly and patent foramen ovale. The STL is similarly displaced downward into the right ventricular cavity.

The displacement of the STL was measured in the four chamber view from the same plane as the anterior mitral leaflet (AML) to the root of the STL in end-diastole using 8 mm cinematography. The displacement ranged from 1.4 to 3.2 cm with an average of 2.1 ± 0.5 cm in eight patients as shown in Table I. However the downward deviation of the STL could not be measured in three patients in the four chamber view. In one of these three patients (M. T.) the rudimentary STL was detected by angulating the probe in the direction B as shown in Fig 1. In contrast the four chamber view disclosed no displacement of

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290 patients Entry into the study was 2 weeks after acute myocardial infarction (AMI) Patients were followed up for 1 year Ventricular arrhythmias totally disappeared in 50% of aprindine patients and in 20% of the placebo group There was no difference in death rate between the two groups Cholestasis (three patients) and agranulocytosis (two patients) appeared in the aprindine group Somewhat similar results have been presented by Hutton using tocainide A comparable study with mexilitine conducted by Julian et al (personal communication 1979) has also shown the same type of result that is reduction or abolition of ventricular arrhythmias compared with placebo therapy but no significant reduction in death rate

Amiodrone

Amiodrone is a Class III drug that is reputed to be effective against ventricular fibrillation It has also been shown to be especially useful in the long term prophylaxis of Wolff Parkinson White syndrome and ventricular arrhythmias but certain side effects (corneal deposits and dysfunction of thyroid gland) have inhibited its general use There is no published information regarding its efficacy compared with any of the preceding new antiarrhythmics

Verapamil

Verapamil a Ca^{++} antagonist is useful in the acute management of supraventricular tachycardias in acute myocardial ischemia or ventricular arrhythmias Once again there have been no comparative trials with verapamil and the other newer antiarrhythmic agents particularly in ventricular arrhythmias

Discussion

The reduction or abolition of ventricular arrhythmias achieved with various drugs such as mexilitine tocainide and aprindine without an accompanying reduction in death rate is rather disappointing indicating that the effectiveness of an antiarrhythmic agent against so called 'warn' or ventricular arrhythmias does not mean that they are effective against VF or sudden death On the other hand it is interesting to note that effectiveness against sudden death in postinfarct patients has been claimed for several agents (not regarded as antiarrhythmic agents) such as sulfinpyrazone aspirin and persantin The explanation

for this divergence of results remains to be elucidated

Summary

A number of new antiarrhythmic drugs have been introduced in the past decade They have been extensively studied mainly in patients with AMI and for short periods following this event No long term comparative trials have been reported although some medium term studies have been completed and longer term studies are underway Most of the new agents have been demonstrated to be effective in diminishing or suppressing serious ventricular arrhythmias but this has not been associated with a corresponding fall in the death rate To date none of these drugs except perhaps beta blockers has been shown to lower the risk of sudden death Nevertheless the question remains as to whether a small reduction in the mortality rate warrants widespread use of any of the current drugs for the prevention of sudden death There is a great need for long term comparative trials with patients properly stratified to see which agent is most effective and in what particular patient group

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Hemodynamic effects of newer antiarrhythmic drugs

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The aim of antiarrhythmic drug therapy is to terminate or suppress specific arrhythmias and improve cardiovascular function. Short term studies of the new Class I drugs encainide, mexiletine and tocainide have demonstrated only minor falls in cardiac index with modest rises in mean aortic pressure. In contrast, disopyramide has been shown to depress myocardial function in both animals and patient studies. Heart failure may be precipitated by therapy with disopyramide and electromechanical dissociation has been reported. Class II agents with beta adrenergic blocking actions all produce a degree of myocardial depression. Atenolol resembles propranolol in patients with coronary artery disease in its hemodynamic effects, whereas acebutolol is less of a depressant, resembling practolol. The Class III agent amiodarone has only a mild depressant effect associated with a reduction in afterload and an increase in coronary blood flow. The Class IV agent verapamil, which is a calcium channel blocker, has potent myocardial depressant actions and causes peripheral vasodilatation. Hypotension, heart failure and shock have been precipitated particularly in patients receiving beta blocking drugs concurrently. While all the new antiarrhythmic drugs currently studied will cause some degree of hemodynamic depression in an appropriately high concentration, present investigations suggest that particular caution needs to be taken when disopyramide, sotalolol, atenolol and verapamil are administered either acutely by the intravenous route or chronically by the oral route.

The aim of successful antiarrhythmic drug therapy is to terminate or suppress a specific arrhythmia and improve cardiovascular function. This action may be achieved by the suppression or termination of arrhythmias that are either directly life threatening or the precipitating cause of cardiovascular failure. An ideal antiarrhythmic drug will achieve this objective without general or cardiovascular side effects in therapeutic dosage. It is important therefore to document the hemodynamic effects of newer antiarrhythmic drugs at clinically relevant concentrations and to confirm that when arrhythmia termination is achieved cardiovascular function is not compromised. These studies need to be performed in patients with heart disease with and without evidence of impaired cardiac function.

In this report the hemodynamic effects of newer antiarrhythmic drugs will be reviewed in

groups according to their predominant experimental electrophysiologic effect as described in the classification of antiarrhythmic drugs by Vaughan Williams¹ and Singh and Vaughan Williams.

Drugs with Class 1 antiarrhythmic action

Mexilitine The influence of mexilitine on left ventricular ejection in patients with abnormal left ventricular function was assessed in patients with implanted Starr Edwards aortic valve prostheses. The duration of aortic bill travel time measured as the QA₁ interval is a measure of left ventricular ejection velocity and was used as an index of myocardial performance. With myocardial depression the QA₁ interval lengthens. Shaw showed that mexilitine in doses from 50 to 150 mg given intravenously over 2 minutes prolonged the QA₁ interval in a dose-related manner over the range 50 to 150 mg and this effect was apparent immediately. It was equal to that produced by equivalent doses of lignocaine indicating similar effects on left ventricular function. Brinn et al.¹¹ in a study of 10 male patients with coronary artery disease found

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an infusion of 15 mg/kg mexilitine had minor effects on cardiovascular hemodynamics only. There was a small but significant rise in left ventricular end-diastolic pressure. During hand grip isometric exercise there were small but significant falls in cardiac output and peak left ventricular dP/dt associated with a small increase in left ventricular end-diastolic pressure. This lack of major hemodynamic effect was confirmed in studies of 16 patients with valvular heart disease. In contrast Saunamäki¹ observed further impairment of myocardial function in three of six patients with ischemic heart disease and previous heart failure who were given mexilitine intravenously achieving a plasma level greater than 1 µg/ml.

In many respects mexilitine is comparable to lignocaine hemodynamically when given intravenously. It is concluded that intravenous administration of mexilitine in clinically effective doses produces little or no adverse hemodynamic effects in the absence of clinical evidence of heart failure. When heart failure is present caution is necessary during its intravenous administration. In controlled studies of long term oral mexilitine in the prophylaxis of ventricular arrhythmias over a 3-month period there has been no evidence that cardiac failure was precipitated.

Disopyramide A negative inotropic effect has been demonstrated when disopyramide is administered intravenously to experimental animals and man. Thus in a placebo controlled study in 18 patients with recent myocardial infarction 100 mg of disopyramide intravenously over 5 minutes significantly prolonged the pre-ejection period and increased the ratio of the pre-ejection period to left ventricular ejection time for more than 15 minutes following drug administration. However if the rate of administration of the same dose was prolonged over 10 minutes a reduced effect was seen.

In a study of 10 patients with cardiac disease (six with normal and four with abnormal left ventricular function) 15 mg/kg of intravenous disopyramide over 2 minutes decreased cardiac index, stroke volume and stroke work index to a greater degree in those patients with abnormal function both during spontaneous sinus rhythm and when heart rate was maintained stable by atrial pacing.

In a recent study electromechanical dissociation has been reported following the administration

of disopyramide to patients with severe congestive failure and renal insufficiency in whom the drug was being administered to control recurrent and resistant ventricular tachycardia. This indicated the need for dosage reduction in the presence of renal insufficiency and extreme caution. The importance of hemodynamic depression following disopyramide administration was demonstrated when 16 patients with disopyramide induced cardiac decompensation were reported out of a total of 100 patients consecutively treated with the drug.

Whereas in patients without established left ventricular dysfunction disopyramide is relatively safe orally the intravenous route should be used with caution. In the presence of left ventricular dysfunction disopyramide is potentially a hazardous agent not only intravenously but also during chronic oral therapy and careful clinical observation is mandatory.

Tocamide In a study of 12 patients with established heart disease 11 of whom had compensated left ventricular dysfunction small increases in left ventricular end diastolic pressure have been noted although no major depression of overall ventricular function was seen with tocamide plasma concentrations within the known therapeutic range. An increase in systemic and pulmonary arterial pressure was observed in this study secondary to increases in vascular resistance in both beds. In patients with valvular heart disease studied echocardiographically in a control study of oral tocamide no evidence of myocardial depression was observed.

Tocamide therefore like lignocaine and mexilitine appears to cause minimal myocardial depression at therapeutic plasma concentrations. Further information on the hemodynamic effects of tocamide are reported elsewhere in this symposium.

Encainide This new antiarrhythmic agent has been shown electrophysiologically to have important Class I actions.² Hemodynamically it has been studied in patients at the time of catheterization by Harrison.³ In this study 17 patients were given encainide intravenously 12 of whom had coronary artery disease and 5 of whom had primary myocardial disease. There was a significant increase in heart rate and systemic vascular resistance following encainide 0.9 mg/kg body weight intravenously with a modest decrease in cardiac and stroke index. Left ventricular end

II Evaluation of antiarrhythmic drugs in acute myocardial infarction

Placebo controlled study of prophylaxis of ventricular arrhythmias in acute myocardial infarction

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Successful prophylaxis of ventricular arrhythmias in acute myocardial infarction might achieve a major reduction in mortality of this condition. No satisfactory drug is yet available but many new antiarrhythmic agents are being tested in this role. Such placebo controlled investigations in the earliest phase of myocardial infarction encounter unique problems of study design, drug pharmacokinetics, study conduct and data analysis.

Identification of a safe effective antiarrhythmic drug for the prophylaxis of ventricular arrhythmias associated with acute myocardial infarction is currently an important goal of cardiologic research. A placebo controlled study is generally considered the optimal design for evaluation of new therapies and is probably essential in this clinical situation which is associated with high natural mortality and morbidity rates but the complex and rapidly changing pathophysiology of acute myocardial infarction presents particular difficulties in the design, conduct and analysis of placebo controlled investigations.

Objectives and justification of placebo controlled studies

The aim of a placebo controlled study for the prophylaxis of ventricular arrhythmias in acute myocardial infarction is to define an antiarrhythmic drug which by preventing serious ventricular arrhythmias might improve morbidity or mortality rates. Ventricular fibrillation and hemodynamically significant ventricular tachycardia are the arrhythmias of particular importance in this

context. The study should clearly identify patients for whom therapy was beneficial and evaluate drug safety in all treated individuals.

Administration of a placebo to patients with acute myocardial infarction is acceptable only if there is no active agent of proved benefit that is being withheld because of the study. Propranolol, lidocaine and disopyramide have been reported to reduce the mortality rate in acute myocardial infarction. Further investigations with propranolol failed to confirm the original findings. The study of intramuscular lidocaine was flawed by a statistically significant excess of patients who received active therapy and a further investigation of lidocaine given by this route failed to show benefit. The findings of the study of disopyramide have been the subject of considerable criticism and cannot be accepted until further corroborative investigations are reported.

A statistically significant reduction of primary ventricular fibrillation by means of high dose intravenous lidocaine has been reported. The hospital mortality rate was unaffected. Although there is no corroborative controlled study, evidence uncontrolled investigations appear to support the original conclusions. However, an earlier investigation using intravenous lidocaine documented an increased evidence of A-V conduction disorders producing prolonged ventricu-

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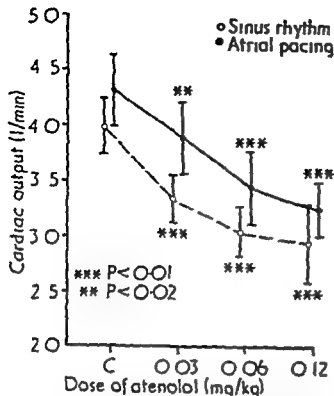


Fig. 1 Mean changes in cardiac output in patients receiving graded doses of atenolol during sinus rhythm and during atrial pacing at a constant rate (From Robinson C Jackson PG Fisk CJ with DF Haemodynamic effects of atenolol in patients with coronary artery disease *Br Heart J* 40 22-8 1978)

diastolic pressure fell significantly. Changes in cardiac index were most marked in the nine patients with low control cardiac index levels. The mild depression seen mainly in patients with impaired cardiac function at rest suggests that this drug's hemodynamic effects will not detract from its potential value. However more information is required on the effects of this drug intravenously and orally on systemic and coronary hemodynamics in patients with established heart disease with and without prior left ventricular dysfunction.

Drugs with Class 2 antiarrhythmic actions

The hemodynamic effects of propranolol have been extensively investigated in the past and it has become the agent against which all new Class 2 antiarrhythmic drugs with beta blocking actions are compared. Hemodynamically practolol has been shown intravenously to be an effective antiarrhythmic drug producing less hemodynamic depression. However development of the oculomucocutaneous syndrome following oral use has restricted its subsequent therapeutic value

although it remains a useful agent intravenously in intensive and coronary care units. Several new beta adrenergic blocking drugs all with comparable antiarrhythmic value particularly in the management of supraventricular arrhythmias have been introduced. Here attention will be limited to two such agents atenolol and acebutolol.

Atenolol Atenolol has been shown to possess cardioselectivity equivalent to that of practolol and like practolol atenolol lacks membrane-stabilizing properties. In contrast however atenolol does not possess intrinsic sympathomimetic activity. Its antiarrhythmic efficacy has been established in animal studies. Its hemodynamic effects have been studied in a group of eight patients with established obstructive coronary artery disease.¹

A dose related decrease in heart rate and cardiac output was shown to be produced without a significant change in systemic arterial pressure when atenolol, 0.03 to 0.12 mg/kg body weight intravenously was given over a total of 5 to 15 minutes (Fig. 1). However in contrast to the previous findings with practolol and like those observed with propranolol there was a significant fall in cardiac output after atenolol which was not purely rate dependent (Fig. 1). Left ventricular end diastolic pressure did not change significantly but there was a dose related reduction in the maximum rate of rise of left ventricular pressure (dP/dt) after atenolol. Systemic vascular resistance increased significantly after atenolol in the patients at rest and this is comparable to the findings after intravenous propranolol but contrasts with those after intravenous practolol in similar patients.¹

The overall hemodynamic effects of atenolol therefore more closely resemble those of intravenous propranolol than those of intravenous practolol. It seems likely that the relatively minor hemodynamic effects that follow intravenous practolol reflect the combination of cardioselectivity and intrinsic sympathomimetic activity of the same agent whereas cardioselectivity alone as in atenolol results in hemodynamic effects similar to those of propranolol. Atenolol is therefore of potential value as an antiarrhythmic drug orally but does not have the hemodynamic advantages of practolol for intravenous administration.

Acebutolol Acebutolol is a new beta adre-

lar systole in lidocaine treated patients who were suspected of having sustained infarction but in whom this diagnosis was not later confirmed.¹¹

The lack of a safe effective antiarrhythmic drug for the prophylaxis of ventricular arrhythmias in patients suspected of acute myocardial infarction justifies continued placebo controlled studies of prophylactic antiarrhythmic therapy.

Study design

Study population In clinical practice an acceptable effective drug for the prophylaxis of ventricular arrhythmias would be given to a relatively unselected patient population with suspected acute myocardial infarction. However the high early incidence of ventricular arrhythmias in acute myocardial infarction¹ allows identification of patients who are at particular risk and therapy may be more economically evaluated by restricting administration to this group.

Shock, cardiac failure and conduction disorders are common reasons for exclusion of patients from studies. It is probably not justified to expose such patients to the risk of antiarrhythmic therapy that may aggravate these complications of acute myocardial infarction. Other acceptable conditions of exclusion include situations where the pharmacokinetics of the drug may be grossly abnormal, e.g. in patients with hepatic or renal disease. Care must be exercised to minimize the exclusion criteria or therapy will be evaluated in such a restricted patient population that the findings will have little practical applicability.

Predefined serious ventricular arrhythmias (ventricular fibrillation and hemodynamically significant ventricular tachycardia), death and possible unwanted effects of therapy or infarction are premature end points of study and usually involve withdrawal of the patient. Patients who are protocol violations should also be withdrawn when it is recognized that they have not satisfied the entry criteria. They will have received inappropriate therapy and it is essential that any consequences of drug administration to them be reported. Nonconfirmation of infarction is the most common cause for early withdrawal. This is usually unavoidable as it is desirable that selected patients be admitted into the investigation as soon as possible after identification. However within the first few hours after the onset of

symptoms definite confirmation of acute myocardial infarction is available for only a few patients since the ECG often will show no or nonspecific ST changes and enzyme levels are not usually available instantly. In consequence a placebo controlled study employing early randomization of patients will probably include a sizable proportion who in retrospect have no sustained acute myocardial infarction but whose progress in the study cannot be neglected.

Therapeutic considerations Prophylactic interventions against serious ventricular arrhythmias, particularly primary ventricular fibrillation, must be rapid in their onset. In theory intravenous administration of a drug could achieve near instantaneous therapeutic plasma levels but in practice this is difficult to accomplish and toxic effects are often encountered. An additional disadvantage is the need for skilled medical or paramedical attendance to establish this route of administration. By contrast intramuscular administration can be undertaken by unskilled people and even by the patient himself with a pressurized injector and by using a suitable site therapeutic plasma level can be obtained almost as quickly as with intravenous therapy. The maintenance of an adequate plasma level of the drug after the initial intramuscular administration can present difficulties and may involve additional intramuscular administration or recourse to either intravenous or oral dosing. Oral therapy has the attraction of easy administration but gastrointestinal absorption may be slow and reduce the effectiveness of the drug. Both acute myocardial infarction and the management of its pain by narcotic analgesics reduce the rate of gastric emptying thus delaying drug absorption.¹¹ This factor probably precludes the successful use of oral antiarrhythmic therapy in reducing the incidence of serious ventricular arrhythmias in acute myocardial infarction.

The duration of administration of therapy can vary from a few hours to many days or even months. If the prophylaxis of primary ventricular fibrillation is the major objective of the study then the duration of therapy might be confined to the first 24 hours after the onset of symptoms since thereafter the incidence of this arrhythmia is low. Continuation of therapy beyond the first 24 hours after the onset of symptoms permits examination of the drug's effect on the arrhythmia.

CORONARY HAEMODYNAMIC EFFECTS OF INTRAVENOUS AMIODARONE IN DOGS

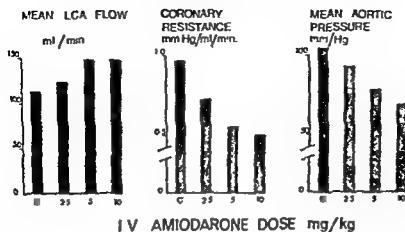


Fig 2 Mean coronary hemodynamic changes following graded doses of intravenous amiodarone in adult open-chest anesthetized dogs. LCA = left coronary artery

ergic blocking drug that has been shown to be approximately one-eighth as potent as propranolol as a beta antagonist. It exerts membrane stabilizing effects similar to those of propranolol. It does have a degree of cardioactivity and also some intrinsic sympathomimetic activity, although less marked than that seen with practolol. Hemodynamically in doses of 0.5 to 1 mg/kg, it has been shown to cause modest reductions in cardiac output and aortic flow when administered postoperatively to patients who have undergone coronary artery bypass surgery.

In a recent study in patients with obstructive coronary artery disease, practolol in doses of 0.6 mg/kg body weight intravenously given over 2 minutes produced only minor systemic hemodynamic effects. The changes in coronary sinus blood flow and coronary vascular resistance were also minor and there was no significant change in myocardial oxygen consumption. It is important to note that the lactate extraction ratio in these patients during control arterial perfusion to the lungs was $-14 \pm 4.5\%$, indicating lactate production. This was reversed to lactate extraction with a mean value of $30 \pm 2\%$ at the same arterial perfusion rate after the drug. Acetazolol therefore resembles practolol more closely than propranolol or atenolol hemodynamically. It is likely that this reflects the presence of both weak intrinsic sympathomimetic activity and cardioselective properties. It is a useful alternative to practolol

when an intravenous beta blocking drug is indicated for the termination of supraventricular arrhythmias.

Drugs with Class 3 antiarrhythmic actions

Amiodarone: Amiodarone, originally introduced as an antineoplastic drug, is the principal agent with Class 3 properties and possesses unique electrophysiologic properties. Its antiarrhythmic effects were summarized by Poenik et al. The effects of amiodarone on cardiac and coronary hemodynamics were studied in open-chest anesthetized dogs by Singh et al. Intravenous amiodarone over the concentration range of 2.5 to 10 mg/kg body weight produced a dose-related decrease in heart rate and to a lesser degree in peripheral resistance with a decrease in cardiac contractile force and left ventricular dP/dt. Despite this, the left ventricular cardiac output increased progressively. No significant fall in left ventricular end-diastolic pressure occurred up to a dose of 5 mg/kg body weight. Intravenously, at 10 mg/kg intravenously, there was a decrease in left ventricular filling pressure occurred. These findings in association with the fall in left ventricular contractile force and left ventricular dP/dt suggested a modest negative inotropic effect. The increase in cardiac output with decreasing peripheral resistance may be mediated by a reflex increase in left ventricular stroke volume which results from the decrease in afterload.

mias encountered in this later phase of infarction but few of these rhythm disturbances will be of a life threatening type

Conduct of the study

Informed consent The value and medicolegal significance of informed consent is controversial¹ but is essential and appropriate for the majority of clinical research investigations. Nonetheless it is questionable whether it is justified to seek informed consent from patients with acute myocardial infarction when they require rest, sedation, relief of pain and reassurance rather than an academic discourse on the implications of enrollment into a placebo controlled prophylactic antiarrhythmic drug study. Informed consent implies a patient's understanding of the conventional alternative to the proposed study. However, there is no standardized arrhythmia management: high dose prophylactic intravenous lidocaine, aggressive treatment of warning arrhythmias and management only of hemodynamically significant arrhythmias are three diverse but widely practiced approaches.² Perhaps in acute myocardial infarction, protocol approval by fellow practitioners and ethical committees, extensive elective drug testing in a variety of clinical situations³ and the propriety and compassionate concern of the investigating physician could reduce the necessity for informed consent.

Arrhythmia data acquisition and analysis As the early high mortality rate of acute myocardial infarction largely reflects primary ventricular fibrillation, it is possible to design a study that does not require continuous recording or monitoring of the ECG. However, most studies do employ some form of ECG analysis. Following the demonstration of the inaccuracy of observer monitoring of the ECG,⁴ continuous ECG recording and sophisticated analysis is commonplace. These recordings can present particular analysis difficulties as the changing shape of the QRS, ST and T waves associated with acute infarction can cause false triggering of arrhythmia analyzers which must also cope with a high incidence of artifact due to the restlessness of the patient, sweating and poor adhesion of electrodes. Continuous ECGs must contain clear identification of at least the time of drug administration and should preferably record clock time continuously throughout the study.

Use of drugs The study medication would be the only drug administered in an ideal prophylactic antiarrhythmic investigation, but in practice this is rarely the case. Restriction of the use of additional antiarrhythmic therapy is however highly desirable. The role of the coronary care unit in the monitoring and rapid treatment of significant arrhythmias assumed greater importance with the suggestion that a variety of ventricular arrhythmias appeared to predict the development of ventricular fibrillation and that suppression of these events could abort ventricular fibrillation.⁵ Were this true, then aggressive suppression of these ventricular arrhythmias would be justified and the task of evaluating drugs for the prophylaxis of ventricular fibrillation might be made easier as reduction of these events could be a criterion of drug effectiveness. However, warning arrhythmias appear not to foretell ventricular fibrillation and have been reported as frequently in patients who do not progress to ventricular fibrillation as in those who do.⁶ The justification for treating these arrhythmias then is their hemodynamic consequence which is probably insignificant for isolated ventricular ectopic complexes of almost any frequency, multiform ventricular ectopic complexes, ventricular ectopic complex pairs, R on T ventricular ectopic complexes and perhaps short runs of ventricular tachycardia. If these arrhythmias can be tolerated without treatment, the attendant reduction in use of antiarrhythmic drugs would greatly improve the evaluation of prophylactic antiarrhythmic drugs. Sustained or hemodynamically significant ventricular arrhythmias such as ventricular fibrillation or prolonged episodes of ventricular tachycardia require treatment when they occur.

Other hemodynamically significant arrhythmias that may require intervention include atrial fibrillation, atrial flutter, sinoatrial disorders and A-V conduction problems which can be a consequence of infarction but which should be considered as potential unwanted effects of the study medication. Similarly, bundle branch block and QRS complex axis shifts should be noted although attitudes vary regarding the need for immediate management or for withdrawal from a prophylactic antiarrhythmic drug study.

Antiarrhythmic drugs are not the only drugs that can interfere with the evaluation of antiar-

Direct intracoronary injections of amiodarone 0.25 to 4 mg which were doses too small to exert systemic effects produced a dose related increase in coronary blood flow associated with a fall in coronary vascular resistance. This coronary vasodilator effect was also seen during intravenous amiodarone injections in doses of 2.5 to 10 mg/kg body weight. In this instance the increasing coronary blood flow and fall in coronary vascular resistance was achieved despite a fall in systemic arterial pressure (Fig 2). Experimentally therefore amiodarone creates a favorable balance in oxygen supply and demand by affecting the major determinants of myocardial oxygen consumption. These experimental observations have since been confirmed in 16 patients undergoing coronary arteriography for chest pain 14 of whom had obstructive coronary artery disease.

These clinical studies therefore confirm that amiodarone used intravenously is a powerful systemic and coronary vasodilator and is relatively safe for use in the acute therapy of patients with cardiac arrhythmias. However antiarrhythmic therapy with amiodarone is generally indicated and most effective by the oral route. To date long term hemodynamic studies using this route of administration have not been published however there are no reports of cardiac failure being precipitated.

Drugs with Class 4 antiarrhythmic actions

Verapamil The prototype of this group of agents that selectively inhibit membrane transport of calcium is verapamil. It is a synthetic papaverine derivative initially introduced as a smooth muscle relaxant which has potent peripheral and coronary vasodilator actions. In isolated heart muscle it does not exhibit Class 1, 2 or 3 electrophysiologic actions and therefore a separate category of action emphasizing the antagonism of the slow inward calcium currents was proposed. Its main locus of action appears to be superficially located membrane storage sites for calcium. In clinical electrophysiology its primary site of action is on the A-V node where A-V conduction time is increased due to depression of the slow response fibers.

Verapamil has a marked negative inotropic effect on isolated heart muscle. In man the most comprehensive study of its hemodynamic effects was reported by Singh and Roche. In 20 patients with coronary artery disease or rheumatic valve

lesions they found the peak effects of intravenous verapamil in a dose of 10 mg occurred between 3 and 11 minutes after the completion of the injection and had disappeared by 10 minutes. Mean arterial pressure and systemic vascular resistance fell significantly with an increase in left ventricular end-diastolic pressure and a reduction in left ventricular dp/dt_{max} . Heart rate and cardiac index increased but these changes were not statistically significant. These results therefore indicated that intravenously verapamil does have a negative inotropic effect but it is minimized by its peripheral vasodilator action in reducing afterload. Caution is clearly necessary particularly when verapamil is administered to patients with significant myocardial decompensation and in patients with myocardial infarction as in these patients there are little data available on the hemodynamic effects of the drug.

The incidence of hemodynamic side effects is much higher in patients previously on beta adrenergic blocking agents who are given verapamil either intravenously or orally. The negative inotropic actions and depressant effects on impulse generation of the beta blocking agents and those of verapamil summate. Severe hypotension coupled with bradycardia and asystole may result.

The administration of verapamil intravenously is therefore potentially hazardous in the presence of impaired left ventricular function and particularly where prior administration of beta adrenergic blocking drugs has been employed. In the absence of left ventricular impairment the mild hemodynamic changes observed are unlikely to be clinically important.

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rhythmic therapy. The variety of clinical problems encountered in acute infarction encourages the use of drugs and if those commonly administered narcotic analgesics diuretics potassium supplements anticonvulsants hypnotics sedatives tranquilizers atropine digoxin and beta adrenergic blocking drugs may all modify the natural course of ventricular arrhythmias, including ventricular fibrillation and may alter the effect of the antiarrhythmic drug under investigation. Many protocols have failed to standardize or establish criteria for the use of these therapies and often reports have omitted information regarding the incidence of use of these drugs during the study.

Termination of the study. At the termination of a prophylactic controlled study all data of all patients should be analyzed before allocation codes are broken unless a sequential statistical approach has been adopted. A theoretic possibility exists that a patient who has received active therapy may be at particular risk of arrhythmias on termination of therapy either by exposure of a previously suppressed event or by a rebound phenomenon. Clinical experience suggests that this problem is not significant.

Analysis of data

Group comparability. The many risk factors related to the natural history of acute myocardial infarction should be balanced in both placebo and active therapy groups. Age, sex, site of acute myocardial infarction, time from onset of symptoms to inclusion in the study, estimates of infarct size, smoking history, the number of previous myocardial infarctions, and previous therapy are among those commonly examined. The time from the onset of symptoms to inclusion in the study is probably the most important feature and is usually recorded for each group as a mean time with the standard deviation. However, this type of comparison is in itself an important imbalance between patient groups and these are relevant in considering ventricular arrhythmias which are critically time dependent. A profile of the number of patients admitted within defined time period from the onset of infarction would allow better comparison.

Analysis of patients who have not sustained acute infarction. All patients in a placebo controlled study of antiarrhythmic drugs in acute myocardial infarction should be

in the final analysis. Those who are entered and who are shown not to have sustained acute myocardial infarction will have received inappropriate therapy. It might be anticipated that an active drug would have little or no beneficial effect in these patients who probably have a low risk of developing serious ventricular arrhythmias, but these individuals may be particularly susceptible to the adverse effects of the study drug. In addition, the dose and route of administration of the active drug will have been chosen to achieve rapid therapeutic plasma levels in patients with acute myocardial infarction but the pharmacokinetics of the drug may be markedly different in patients without this diagnosis. Analysis of nonmyocardial infarction patients should include documentation of the incidence not only of unwanted symptoms but also of cardiac failure, sinus bradycardia, and conduction disorders, shock, and analysis of ventricular arrhythmias as performed for those patients with definite acute myocardial infarction.

Extrapolation of results. Although tempting, it is not justified to extrapolate that a drug highly effective in suppressing ventricular tachycardia will be useful in the prevention of ventricular fibrillation. Primary ventricular fibrillation and ventricular tachycardia have distinctly different time courses in acute myocardial infarction and their mode of initiation is strikingly different.

Conclusions

Since 1961 there have been over 14 placebo controlled studies of antiarrhythmic therapy in acute myocardial infarction. The drugs investigated have included procainamide, quinidine, propranolol, lidocaine, disopyramide, mexiletine, and tocainide. Few have restricted inclusion to patients seen in the early hours of infarction and analysis of events in nonmyocardial infarction patients has been rare. There is no standardized study design for the placebo controlled investigation of prophylactic antiarrhythmic drug therapy in acute myocardial infarction but improved knowledge of the natural history of arrhythmias in acute infarction and awareness of the practical difficulties and implications of identifying a successful management dictate careful consideration of the many special aspects of research of this clinical problem.

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Comparison of newer antiarrhythmic agents

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In the past decade a number of new antiarrhythmic drugs have been introduced. They have been extensively used in the acute phase of myocardial infarction. Few if any long term comparative trials of these newer agents have been reported. Most of these newer agents have been shown to be able to reduce the frequency of ventricular arrhythmias but not the mortality rate. Beta blockers and some antiplatelet adhesive drugs, however, have reduced the mortality rate following myocardial infarction. There is a need for long term properly stratified trials of these effective agents.

The main aim of chronic antiarrhythmic therapy is to reduce or prevent the occurrence of ventricular fibrillation (VF) and sudden death, thus reducing the mortality rate. Certain antiarrhythmic agents such as quinidine, procainamide and phenytoin have been extensively studied—especially in coronary heart disease where VF and sudden death are most common. Quinidine has been shown to decrease ventricular ectopic beats (VEBs) in acute myocardial infarction, but there is no convincing evidence that it has materially reduced the mortality rate from sudden death in such patients in the long term. In fact, in some patients it has been shown to precipitate VF. In contrast, procainamide does appear to have a favorable effect, not only in reducing the frequency of VEBs but also the frequency of sudden death. A major problem resulting from its long term use, however, is its ability to produce a systemic lupus erythematosus-like syndrome in a large proportion of patients. Phenytoin appears to be less effective than procainamide in preventing serious ventricular arrhythmias.

Furthermore, the numerous studies involving these drugs have shown that the dosage schedule for each drug requires adjustment for each individual patient and side effects are not infrequent. There is therefore a need to look for newer antiarrhythmic agents that not only diminish or

suppress ventricular arrhythmias but also prevent VF and sudden death, have a simple dosage regime and have few or no side effects when taken over a prolonged period.

There is a dearth of information on long term comparative trials of the new antiarrhythmic agents. It is therefore necessary to review the various publications on each agent and thereby try to gain some knowledge about their relative efficacy.

Beta blocking agents

Although beta adrenergic blocking agents have been in use for 10 to 15 years, mainly for the treatment of angina pectoris and hypertension, they may also be regarded as falling into the category of newer antiarrhythmic agents. Propranolol, alprenolol, oxprenolol and propranolol have been used in long term secondary prevention studies following acute myocardial infarction. To date the results of 15 studies in Europe have been reported. In 11 of the studies¹⁻¹¹ the agent was started within 24 to 48 hours of the clinical onset of infarction. In the remaining four studies treatment was started 2 weeks or more after the onset of infarction.¹²⁻¹⁵ It is not possible to summarize in this presentation the results of all of these studies, which varied in design, selection of patients and duration of treatment. Furthermore, the effect of the particular agent on preventing sudden death, as opposed to reinfarction, is not clear from the presentation of results. We propose to discuss briefly the major studies with positive findings.

The results of the multicenter propranolol study

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Hemodynamic and antiarrhythmic effects of tocainide in patients with acute myocardial infarction

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In order to evaluate the hemodynamic and antiarrhythmic efficacy of tocainide studies were performed in patients suffering acute myocardial infarction. Intravenous tocainide was administered over a 15 minute period in order to determine its acute effects and subsequently in a randomized double blind study with placebo control to determine its effects over a 24-hour period in acute myocardial infarction. Tocainide resulted in a significant decrease of frequent and complex ventricular arrhythmias acutely and had only minimal effects of hemodynamics in most patients. In the long term studies tocainide produced no adverse hemodynamic effects when compared with placebos.

Tocainide is a new antiarrhythmic drug that is chemically similar to lidocaine but in contrast is effective in the treatment of ventricular arrhythmias when given orally.¹⁻⁴ Although some of the patients in previously reported studies had coronary artery disease the antiarrhythmic circulatory and adverse effects of tocainide have not been evaluated in patients with acute myocardial infarction (AMI). As tocainide will be used in patients with AMI the present study was performed to evaluate the hemodynamic and antiarrhythmic effects of the drug and patient tolerance in this situation.

Methods

Patients with AMI and frequent (more than five per minute) paired multifocal early premature ventricular contractions (PVCs) and/or ventricular tachycardia (runs of three or more PVCs rate over 100 beats/min) were studied within 24 hours of the onset of symptoms. No antiarrhythmic agents other than tocainide were given before

or during the study period. Bed side catheterization was performed in the coronary care unit (CCU) and the right atrial, pulmonary artery and aortic pressures were recorded continuously. All pressures are given as means of at least five breathing cycles. Cardiac output was determined by the thermodilution technique. Each value representing the mean of at least three consecutive measurements. From the time of admission and during the whole CCU stay a continuous ECG was recorded and reviewed for visual evaluation.

To provide an acute loading dose the first series of patients (Group 1) was given 0.5 mg/kg/min tocainide as a continuous infusion over 15 minutes. The second series of patients (Group 2) received 0.75 mg/kg/min in the same way. Hemodynamic measurements were performed immediately before as well as 15, 30, 45 and 60 minutes after the start of the tocainide infusion. Thirty five minutes after termination of the infusion the patients randomly and double blind received either two 400 mg tocainide tablets (400 mg) or two placebo tablets. Thereafter they received one tablet of either tocainide or placebo respectively every 8 hours for 24 hours. Blood samples for tocainide analysis were collected from one of the catheters at 0, 2, 30, 60, 120 and 180 minutes after the start of the intravenous infusion as well as at 0, 60, 120 and 180 minutes

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well known.¹¹ A total of 3053 patients with myocardial infarction were studied. 1533 given practolol and 1520 received a placebo. Duration of the study was 2 years. There was overall reduction in the death rate including sudden death rate of 38%. The patients with prior myocardial infarction were reported to get the most benefit although the reduction in the death rate was similar in the two groups irrespective of the site of the infarct.

This study has been criticized on several grounds such as it is not possible to assess the representativeness of patients with regard to anterior or inferior infarction without knowing numbers and reasons for exclusion from the study and patients may have been selected as judged by the low total mortality rate. The end point of death and reinfarction were not clearly defined if sudden death is the main end point it may appear to be more important to discriminate according to blood pressure rather than to site of infarction. Some workers have felt that the results presented did not warrant the conclusion that practolol is especially favorable in patients with a specific location of infarction. Unacceptable side effects from long term oral therapy have now precluded the use of this agent. Selinsson et al.¹² reported beneficial results with alprenolol in 230 patients subdivided into treatment and placebo groups each stratified into one of four risk groups. Group I had no previous cardiac damage. Group II had mechanical damage to the myocardium. Group III had previous cardiac damage and Group IV was a combination of Groups II and III. The dose of alprenolol was 400 mg daily and the duration of therapy was 2 years. Patients were entered 1 week after hospital discharge. After this time 11 patients in the placebo group and three in the treated group had died suddenly. A small but significant fall in the sudden death rate resulted from alprenolol therapy. The mechanism of action, however, is not clearly understood whether it is an antiarrhythmic effect or an effect on myocardial metabolism. Similar results have been reported by Ahlmark et al.¹³ using alprenolol. The drug was given in a dose of 400 mg daily, therapy being initiated 24 to 48 hours after the onset of infarction. Expected reinfarction. The trial was continued for 1 year. There was a significant reduction in mortality rate after 1 year in patients under

65 years of age. There was no effect on the short term mortality rate. It was not possible from the data presented to decide whether or not there was a significant drop in the sudden death rate although the results presented so far suggest that practolol and alprenolol reduce the post-infarction mortality rate from sudden death.

It is pertinent to ask whether the widespread use of beta blocker in all postmyocardial infarction patients is justified to achieve such a small percentage of benefit clinically. If one assumes an annual postinfarction mortality rate of 6% and aims at achieving a 30% fall in the mortality rate with beta blocking therapy then only two out of every 100 patients would benefit. Baber et al.¹⁴ with the last point in mind carried out a long term trial in postinfarction patients using propranolol 40 mg daily designed on lines similar to the practolol trial. Their aim was to reduce the mortality rate by 50%. The trial failed to show a positive result.

At present there are a number of long term trials being conducted throughout the world using various beta blockers such as acebutolol, metoprolol, oxprenolol, pindolol, propranolol, sotalol and timolol (Table I). Whether these trials will answer certain questions posed by the practolol and alprenolol trials remains to be seen. Certainly there has been no attempt in these trials to determine whether one beta blocker is superior to another. Also none of these trials will define the mode of action of beta blockers in reducing the mortality rate. Furthermore there does not appear to have been much attempt at stratifying patients to see what groups might benefit most from beta blocking therapy.

Disopyramide

This drug has properties similar to those of quinidine and procainamide although its side effects are somewhat different because they are mainly confined to anticholinergic effects. It has been shown to be as effective as quinidine in reducing ventricular ectopic activity but is claimed to have fewer side effects. Comparative studies of disopyramide with atenolol, mexilitine and placebo have been reported on a small number of patients but the duration of drug therapy was short 1 week for each drug. No chronic comparative studies of disopyramide with other newer antiarrhythmic studies have been reported. It is of interest however that Oshram¹ has been

Table I Patient characteristics

| Case No | Sex | Age (yr) | Previous myocardial infarction | ECG site of infarction | SASAT _{max} (μkat/L) | Time from onset of symptoms to inclusion in study (hr) | Total amount of tocainide in (mg) | Oral tocainide (T) or placebo (P) |
|----------------|-----|----------|--------------------------------|------------------------|-------------------------------|--|-----------------------------------|-----------------------------------|
| Group 1 | | | | | | | | |
| 1 | M | 54 | No | AL | 60 | 12 | 550 | T |
| 2 | M | 58 | No | S | 082 | 12 | 533 | P |
| 3 | M | 66 | Yes | I | 108 | 16 | 570 | T |
| 4 | M | 65 | No | AL | 570 | 6 | 540 | P |
| 5 | M | 61 | No | A | 648 | 16 | 560 | P |
| 6 | M | 64 | Yes | IL | 536 | 20 | 520 | P |
| 7 | F | 73 | No | S | 340 | 9 | 580 | P |
| 8 | F | 71 | No | A | 116 | 12 | 526 | T |
| 9 | M | 68 | Yes | AL | 207 | 23 | 640 | T |
| Group 2 | | | | | | | | |
| 11 | M | 60 | No | L | 177 | 24 | 1000 | P |
| 12 | M | 50 | No | I | 376 | 8 | 800 | I |
| 13 | F | 69 | No | I | 18 | 74 | 640 | I |
| 14 | F | 66 | Yes | A | 100 | 8 | 539 | T |
| 15 | M | 51 | No | ILR | 439 | 5 | 770 | I |
| 16 | M | 72 | Yes | Uncertain | 258 | 12 | 680 | — |
| 17 | M | 66 | No | I | 621 | 17 | 88 | T |
| 18 | M | 58 | No | LS | 167 | 13 | 810 | T |
| 19 | M | 58 | No | A | 126 | 19 | 1090 | T |

Abbreviations: A = anterior; L = lateral; I = inferior; S = subendocardial; R = right ventricular; SASAT_{max} = maximal serum aspartate aminotransferase expressed in micromoles per liter.

after the last oral dose at 24 hours. Patients were questioned carefully to identify subjective symptoms and observed for objective signs of adverse effects. The study code was broken after the hemodynamic, antiarrhythmic and adverse effects had been evaluated in all patients.

Results

Patient characteristics are shown in Table I. There were no significant differences between Group 1 and Group 2 or between the tocainide and the placebo groups with respect to the variables described. All patients were discharged from the hospital alive.

Tocainide plasma concentrations. Tocainide plasma concentrations for the two infusion rates are shown in Fig 1. At 15 minutes the mean plasma concentration for Group 1 patients receiving the 0.5 mg/kg/min dose was 438 ± 134 μmol/L. For Group 2 patients receiving 0.75 mg/kg/min the 15 minute value was 636 ± 134 μmol/L. The mean plasma concentration of the tocainide group at 24 hours immediately prior to the last oral dose was 266 ± 45 μmol/L.

Hemodynamic measurements. The mean and standard deviation of the hemodynamic measurements in all 18 patients are given in Table II. At 15 minutes there was a small but significant increase in heart rate, right atrial pressure, pulmonary artery diastolic pressure, aortic diastolic pressure and systemic vascular resistance. There was also a small but significant decrease of cardiac index, stroke index and left ventricular stroke work index. Immediately before the tocainide infusion there were no statistically significant differences in any of the hemodynamic parameters between Group 1 and Group 2 patients. At 15, 30, 45 and 60 minutes a significantly higher right atrial pressure was recorded in the Group 1 patients. All other hemodynamic differences between the two groups were not statistically significant.

The hemodynamic changes in the tocainide and placebo groups measured after the last oral dose at 24 hours are summarized in Tables III and IV. At 0 minutes, the time of the last dose, there were no statistically significant differences between the tocainide and placebo groups with respect to

Table 1 Trials being conducted with beta blocking agents

| Center | Compound | % of patients | Prognostic stratification |
|------------------------------|-------------|---------------|---------------------------|
| Multicenter France | Acebutolol | 550 | - |
| Stockholm Sweden | Metoprolol | 250 | + |
| Amsterdam Netherlands | Metoprolol | 500 | + |
| Gothenburg Sweden | Metoprolol | 600 | + |
| Multicenter USA | Metoprolol | 3 000 | - |
| Multicenter UK | Oxprenolol | 1 100 | - |
| Multicenter Germany | Oxprenolol | 4 000 | - |
| Multicenter Sweden Australia | Pindolol | 500 | - |
| Multicenter UK | Propranolol | 500 | - |
| Multicenter USA | Propranolol | 4 200 | - |
| O-lo Norway | Propranolol | 500 | - |
| Multicenter North England | Sotalol | 1 600 | - |
| Multicenter Norway | Timolol | 1 800 | + |
| Total | | 19 100 | |

reported to have used disopyramide therapy in 59 patients for 5 years with suppression of ventricular ectopic beats (VEBs) and ventricular tachycardia (VT) in 80% of cases without development of serious side effects. Its effect in preventing ventricular fibrillation (VF) was not reported in this series. Jennings et al. claimed that disopyramide was effective in a controlled myocardial infarction (MI) study in reducing the mortality rate (VF) compared with placebo. This study, however, has been criticized on several grounds. The number of patients studied was small (30 treatment versus 30 placebo); the mortality rate in the placebo group was relatively high; the selection of patients for treatment or placebo group was not clearly defined; a high percentage of patients in the 70 to 80 years of age group appear to have been included; and some patients on disopyramide did not appear to have any drug detectable in their plasma.

Furthermore, in spite of claims that disopyramide is safer than quinidine, serious side effects have been reported. Ross et al.¹² have demonstrated profound hypotension after a single dose and potent depressive effect on A-V node/bundle of His conduction. Podrid et al.¹³ have concluded that disopyramide exerts a profound negative inotropic effect that is unique among antiarrhythmic agents manifesting itself as congestive cardiac failure (CCF). This appears during the first 3 weeks of therapy, but may require several months to develop. They suggest that disopyramide is not indicated in patients with a history of CCF or a past history of CCF. This study is ongoing.

casts a cautionary note over the long term use of disopyramide.

In a short term comparative study recently completed by Hampton et al. (personal communication 1980) involving oxprenolol, disopyramide and placebo in acute infarct patients followed up for 6 weeks, the results are of some interest in view of the preceding comment. (1) There was no significant difference in mortality rates between the three agents. (2) Disopyramide reduced the incidence of ventricular ectopics without affecting the death rate. (3) There was an excess of heart failure in those patients treated with disopyramide, confirming the experience of Podrid et al.¹³

Mexilitine and tocainide

Mexilitine is one of the newer antiarrhythmic drugs tested in recent years. In several studies it has been compared with procainamide, atenolol, disopyramide and tolamolol but mostly on a short term basis. There is good evidence from other studies that it is effective against VFB and VT.¹⁴ While the short term studies indicate that it is at least as effective as procainamide and disopyramide and more effective than atenolol and tolamolol (against ventricular arrhythmias), it has rather frequent side effects. What its relative merits are on a long term basis has not yet been shown.

Two other antiarrhythmic agents have been used and compared with placebo in long term studies—aprinidine and tocainide. The former drug was studied by Hageman et al.¹⁵ It involved

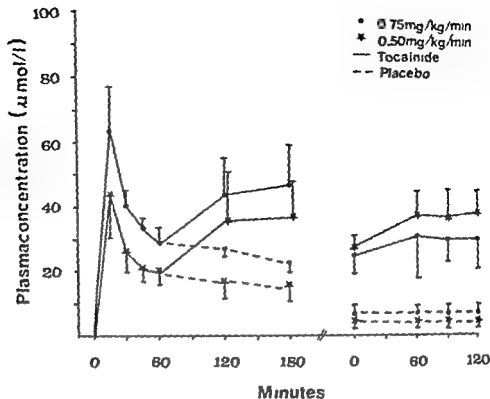


Fig 1 Tocainide plasma concentrations (\pm SD)

Table II Hemodynamic values in all 18 patients (mean and standard deviation)

| Min | HR | RA | PA | PA ₁ | AO | AO | IO ₁ | CI | SI | LVS/L | PRV | Q ₁ R |
|-----|-------|-----|------|-----------------|--------|-------|-----------------|--------|---------|-------|---------|------------------|
| 0 | 21 | 4±3 | 13±4 | 21±6 | 101±2 | 89±13 | 107±16 | 24±0.4 | 3.1±0.8 | 30±19 | 1.8±0.8 | 110±17 |
| 15 | 33±11 | 3±3 | 10±3 | 23±6 | 101±30 | 89±14 | 110±19 | 23±0.4 | 3.1±0.8 | 41±11 | 1.8±0.8 | 110±17 |
| 30 | 41±14 | 3±3 | 14±4 | 21±5 | 103±37 | 83±17 | 110±27 | 23±0.4 | 3.2±7 | 51±1 | 1.8±0.8 | 110±17 |
| 45 | 31±21 | 3±3 | 14±4 | 23±8 | 103±34 | 80±15 | 109±10 | 24±0.3 | 3.4±0.4 | 34±5 | 1.7±0.5 | 110±17 |
| 60 | 31±13 | 3±3 | 13±4 | 21±5 | 103±30 | 84±13 | 117±17 | 24±0.4 | 3.3±0.8 | 30±11 | 1.8±0.8 | 110±17 |

Abbreviations: HR = heart rate (beats/min); RA = mean right atrial pressure (mm Hg); PA = pulmonary artery pressure (mm Hg); PA₁ = pulmonary artery pressure (mm Hg); AO = aortic pressure (mm Hg); CI = cardiac index (l/min/m²); SI = stroke index (ml/m²); LVS/L = left ventricular stroke volume (l/m²); PRV = pulmonary regurgitant volume (ml/m²); Q₁R = aortic regurgitant volume (ml/m²); HR = heart rate (beats/min); RA = mean right atrial pressure (mm Hg); PA = pulmonary artery pressure (mm Hg); PA₁ = pulmonary artery pressure (mm Hg); AO = aortic pressure (mm Hg); CI = cardiac index (l/min/m²); SI = stroke index (ml/m²); LVS/L = left ventricular stroke volume (l/m²); PRV = pulmonary regurgitant volume (ml/m²); Q₁R = aortic regurgitant volume (ml/m²).

any of the hemodynamic parameters. In the tocainide group there was a small but statistically significant rise in the mean aortic pressure from 102 mm Hg at 0 minutes to 103 mm Hg at 90 minutes ($P < 0.05$). No other significant hemodynamic changes were observed. In the placebo group there was an increase of heart rate from 81 beats/min at 0 minutes to 83 beats/min at 45 minutes ($P < 0.05$) and to 84 beats/min at 90 minutes ($P < 0.01$). The mean aortic pressure fell significantly from 102 mm Hg at 0 minutes to 94 mm Hg at 90 minutes ($P < 0.05$). No other significant hemodynamic changes were observed.

In this group No significant differences between the tocainide and the placebo groups were observed at 0, 45, 60 and 90 minutes with respect to any of the hemodynamic parameters.

Antiarrhythmic effects Seven patients had ventricular tachycardia within 1 hour prior to the tocainide infusion compared to one patient during the 1 hour after the start of the infusion ($P < 0.05$). The corresponding figures for multiple PVCs were nine and two patients respectively ($P < 0.05$) and for paired PVC nine and three patients respectively ($P < 0.05$).

Within the nearest 15 minutes prior to the start

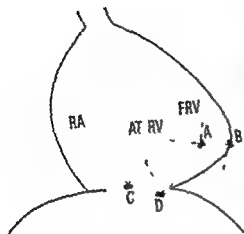


Fig 1 Position of the transducer and direction of the ultrasonic beam. Position A provides an apical four-chamber view and position B shows a three chamber view of the right-sided heart from the apex which is nearly perpendicular to the cross section for the apical four chamber view. Position C provides a horizontal subaphoid cross-section and D indicates subaphoid cross-section along the left costal margin.

the STL in 10 normal subjects and in 10 patients with ASD of secundum type.

Three chamber view. An apical three chamber view was obtained in nine of the 11 patients. Fig 4 shows an example of the three chamber view in the same patient as Fig 2. A remarkable displacement of the STL is visualized whereas the ATL attaches to the original valve ring. Moreover the tricuspid valve ring (TVR) is clearly visualized.

Additionally the chordae tendineae inserting into the ATL were visualized in four instances from the four chamber view and in five cases from the three chamber view respectively.

2 Subaphoid cross-section. We succeeded in recording the subaphoid cross section in nine out of the 11 patients whereas in the remaining two the interpretable images could not be obtained due to liver enlargement or tight abdominal wall. In order to obtain better images from this area we adjusted the gain setting by increasing the intensity of the ultrasonic beam and deepened the focal point.

As a result the right sided heart chambers were widely observed as well as the interventricular septum and the left ventricle. Moreover the elongated ATL was demonstrated clearly from the tip to the root attached to the tricuspid valve ring in eight out of the nine patients. In addition the root of the ATL was remarkably thickened in five. Fig 5 shows a subaphoid cross section taken



Fig 2 Four chamber view by cross section through the apex in a 3-year-old patient with Ebstein's anomaly. Top diastolic picture. Bottom aortic image. The septal tricuspid leaflet is displaced downward into the right ventricle resulting in the formation of the atrialized and functional right ventricles. FRV = functional right ventricle. AT RV = atrialized right ventricle. RA = right atrium. STL = septal tricuspid leaflet. ATL = anterior tricuspid leaflet. LV = left ventricle. IAS = interatrial septum. AVL = anterior mitral leaflet. LA = left atrium. CT = chordae tendineae.

from the same patient as shown in Fig 2. The ATL is fully visualized from the tip to the root attached to the tricuspid valve ring. The chordae tendineae (CT) inserting into the ATL are also discernible. Fig 6 shows another example of the subaphoid cross section in a 5 year old patient (F A). The ATL was fully described from the tip to the thickened root wall as a part of the interventricular septum and the left ventricle. In six patients the CT to the ATL was visualized in the subaphoid cross section. Moreover a hypertrophied anterolateral papillary muscle was also recognized in the subaphoid cross section in one instance.



Fig 3 Another example of the four chamber view in a 21 year old female (A 1) with Ebstein's anomaly and PFO. The STL is displaced into the right ventricular cavity. Abbreviations are the same as in Fig 2.

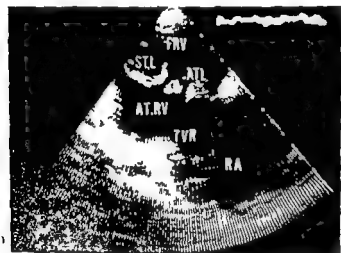


Fig 4 Three chamber view of the right sided heart by cross section through the apex in the same patient as in Fig 2. The functional and atrialized right ventricles and the right atrium were depicted by cross section through the cardiac apex in direction B as shown in Fig 1. Abbreviations are the same as in Fig 2.

In three patients the STL was found to be displaced downward by the subxiphoid approach.

Discussion

Recently cross sectional echocardiography has come into clinical use thus providing useful information on cardiac anatomy and movements. It is suitable for the spatial orientation of the heart structures because of its two dimensional nature.



Fig 5 Subxiphoid cross section taken from the same patient as in Fig 2. The ATL is fully visualized from the tip to the root anchored on the right atrioventricular junction. The chordae tendineae (CT) inserting into the ATL are also discernible. CT = chordae tendineae. Other abbreviations are the same as in Fig 2.



Fig 6 Another example of the subxiphoid cross section obtained from a 4 year old patient (F A) with Ebstein's anomaly associated with patent foramen ovale. The elongated ATL is fully seen from the tip to the thickened root and the right side of the heart is widely visualized. Abbreviations are the same as in Fig 2.

Matsumoto and associates¹⁶ reported on the visualization of the tricuspid valve in Ebstein's anomaly using a mechanical sector scan. However, the probe was too large to be easily manipulated and the apical and subxiphoid approaches were not available. Hirschklau and associates¹ applied a multicrystal echocardiographic system to this lesion to obtain real time observation of the tricuspid valve abnormalities. However, the scanner was not appropriate for the cross section through the subxiphoid area and the problem of

Table III Hemodynamic changes in the tocainide group at the time of the last dose (mean and standard deviation)

| Min | HR | RA | PA | PA | PA _{sw} | AO | AO | AO | CI | SI | LVSWI | PIR | SVI |
|-----|-------|-----|-------|------|------------------|--------|-------|--------|--------|------|-------|--------|---------|
| 0 | 84±18 | 4±2 | 33±13 | 14±6 | 23±10 | 139±20 | 76±14 | 102±17 | 96±0.5 | 31±2 | 45±8 | 18±0.9 | 0±0.4 |
| 40 | 83±19 | 4±2 | 33±11 | 14±7 | 22±10 | 14±79 | 80±16 | 100±17 | 96±0.3 | 32±2 | 48±12 | 19±1.0 | 213±4.8 |
| 60 | 84±17 | 4±2 | 32±12 | 14±6 | 21±11 | 141±94 | 78±13 | 104±17 | 96±0.3 | 32±4 | 49±8 | 18±1.1 | 209±5.2 |
| 90 | 84±18 | 4±3 | 37±11 | 13±8 | 22±12 | 143±94 | 79±14 | 100±17 | 26±0.3 | 32±0 | 47±17 | 18±0.8 | 212±4.4 |

For abbreviations, see Table II

P<0.05

Table IV Hemodynamic changes in the placebo group at the time of the last dose (mean and standard deviation)

| Min | HR | RA | PA | PA | PA _{sw} | AO | AO | AO _{sw} | CI | SI | LVSWI | PIR | SVI |
|-----|------|-----|-------|------|------------------|--------|-------|------------------|--------|------|-------|--------|---------|
| 0 | 81±5 | 4±4 | 9±13 | 10±6 | 18±6 | 130±17 | 74±11 | 99±12 | 27±0.4 | 34±6 | 49±14 | 16±0.7 | 188±1.3 |
| 40 | 80±6 | 4±4 | 29±13 | 9±4 | 17±6 | 127±16 | 2±12 | 90±11 | 27±0.4 | 37±5 | 43±14 | 16±0.7 | 187±1.5 |
| 60 | 86±7 | 4±4 | 78±13 | 9±4 | 16±6 | 12±15 | 72±10 | 94±10 | 77±0.3 | 32±4 | 44±10 | 16±0.7 | 183±1.8 |
| 90 | 86±7 | 4±4 | 21±12 | 9±4 | 16±6 | 126±10 | 7±11 | 94±10 | 2±0.3 | 32±5 | 43±17 | 15±0.7 | 178±1.7 |

For abbreviations, see Table II

P<0.05

P<0.01

of the tocainide infusion four patients had more than five PVCs per minute. A reduction of the number of PVCs was seen in all four patients during 60 minutes following the start of the infusion. There were no statistically significant differences between the tocainide and placebo groups during the tablet administration period with respect to the incidence of ventricular tachycardia, multifocal PVCs, or paired PVCs. The number of PVCs in the tocainide group was significantly higher than the number in the placebo group during both the pretreatment period ($P<0.01$) and the treatment period ($P<0.001$). One patient in the placebo group (Case 7) developed ventricular fibrillation 4 hours after the start of the tocainide infusion (plasma concentration at this time 18.7 µmol/L).

Adverse effects In association with the intravenous infusion, six patients in each group had no adverse effects at all. Eight patients in each group reported a cool throat and a fresh taste of mint which was described as pleasant or unpleasant between 5 and 10 (mean 8 ± 2) minutes after the start of the infusion. The difference was noted between 4 and 30 minutes. A correlation was found between plasma concentration of tocainide and side effects. Two patients reported lightheadedness and two had one episode of vomiting.

Table V Adverse effects during the tocainide/placebo tablet period

| Adverse effects | Tocainide group | Placebo group |
|-----------------------------|-----------------|---------------|
| No adverse effects | 5 | 5 |
| Nausea | 1 | 1 |
| Vomiting | 1 | 2 |
| Generalized warmth | 0 | 1 |
| Bradycardia and hypotension | 1 | 0 |

35 minutes after the start of the infusion. Three patients (Cases 3, 16, and 19) had bradycardia and hypotension 20, 25, and 30 minutes after the start of the tocainide infusion. They were easily treated by a head down posture in two patients and atropine in the third patient with prompt disappearance of symptoms. No significant differences between the tocainide and placebo groups were observed during the long term tablet administration period with respect to adverse effects (Table V).

Discussion

The new antiarrhythmic drug tocainide is effective against ventricular tachyarrhythmias when given both intravenously and orally. The effect seems to correlate with the concentration of drug in the plasma and a therapeutic range of 18 to 40

Tocainide for refractory ventricular arrhythmias of myocardial infarction

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Oral tocainide was used as a long term antiarrhythmic in patients with symptomatic high-grade ventricular ectopic activity refractory to conventional antiarrhythmic agents. Eleven of the 22 patients had a previous myocardial infarction (three patients had a ventricular aneurysm). Unacceptable side effects precluded long term use of tocainide in two patients. Long term tocainide was effective in six of the remaining patients for periods of 9 days to 42.5 months (mean 15.2 months). Eight of these nine patients responded to intravenous lidocaine prior to tocainide therapy.

Chronic antiarrhythmic therapy with tocainide was evaluated in 22 patients with symptomatic high grade ventricular ectopic activity (10 with life threatening ventricular tachycardia) resulting from a variety of cardiac diseases. The arrhythmias were refractory to all currently available antiarrhythmic agents in the United States both singly and in combination. Eleven of the 22 patients had a previous myocardial infarction. Unacceptable side effects precluded use of tocainide in two patients hence the experience in the remaining nine patients with previous cardiac infarction forms the basis of this report.

Material and methods

Twenty two patients with refractory symptomatic high grade ventricular ectopic activity (VEA) including 10 patients with symptomatic ventricular tachycardia (VT) were considered for tocainide therapy. Eleven of the 22 patients had a previous myocardial infarction and long term experience with nine of these patients forms the basis of this report (Table I). Three of these nine patients had a documented ventricular aneurysm and six of the nine patients had VT. The ages of the nine patients ranged from 28 to 42 years

(mean 54 years) eight patients were male. Tocainide was employed chronically in these nine patients for 0.3 to 42.5 months (mean 25.5 months).

All nine patients had been previously treated with conventional antiarrhythmic agents available in the United States. In the majority of the patients adequate plasma levels of these agents were achieved before their lack of efficacy was accepted. The drugs were used singly and in combination or were considered to be contraindicated before tocainide therapy was instituted. Of the agents used (Table II) quinidine was ineffective in all nine patients. Procainamide was used in seven patients and found to be ineffective in five, produced lupus erythematosus in two and was contraindicated in one patient. Disopyramide was ineffective in two of the five patients in whom it was used and had to be discontinued because of unacceptable side effects in the remaining three (60%) patients. Disopyramide was contraindicated in three patients and not commercially available for use in one patient. Propranolol was ineffective in five of the nine patients in whom it could be used.

Oral tocainide was begun after discontinuation of all previous antiarrhythmic agents with the exception of lidocaine. It was initially employed at 400 mg every 6 to 8 hours and more recently at a dose of 600 mg every 8 to 12 hours. The dosage was increased every 24 to 48 hours until acceptable arrhythmia control or unacceptable side

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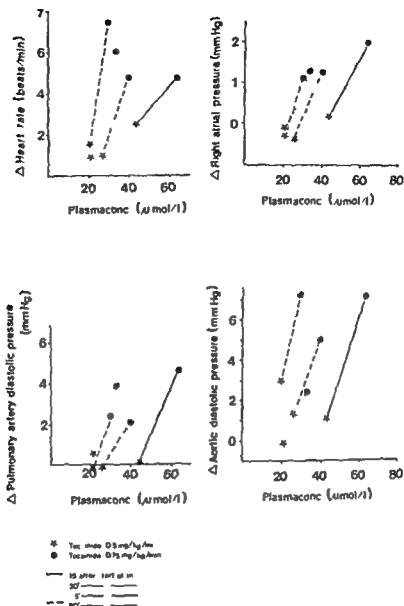


Fig 2 Changes in heart rate, right atrial mean pressure, pulmonary artery diastolic pressure, and aortic diastolic pressure in relation to plasma concentration of tocamide and two infusion rates

μmol/L has been suggested. In the present study only one of the Group 1 patients was slightly below the recommended therapeutic interval during the 45 minutes after the tocamide infusion. On the other hand, five of the Group 2 patients had plasma concentrations rather high above the suggested therapeutic range at 15 minutes after the start of the infusion. Until the therapeutic range has been definitely settled, the data from the present investigation suggest that an infusion rate of 0.5 mg/kg/min may be sufficient in patients with AMI. Plasma concentrations were well within the suggested therapeutic range with the dosage regimen of 0.5 mg/kg/min followed by 400 mg tid used in the present study.

The patients participating in the present study all had AMI with onset of symptoms within 24 hours prior to the tocamide infusion. Some of the patients had considerable left ventricular dysfunction, cardiac indices varying between 1.7 and 3.1 L/min/m², pulmonary artery diastolic pressures varying between 4 and 20 mm Hg, and/or right ventricular failure with mean right atrial pressures varying between 0 and 11 mm Hg. Intravenous tocamide was well tolerated hemodynamically by all patients but three. Although statistically significant, the hemodynamic changes were small. In all 18 patients the mean change at 15 minutes was an increase in heart rate of 3 beats/min (4%) in mean right atrial

Table I Summary of patients on long term tocainide therapy

| Sex | Age | VA | Duration of therapy (mo) | Tocainide dose (mg/day) | Dosing interval (hr) | ET induced before tocainide | VEA during tocainide | VT | | Lown grade | |
|-----|-----|-----|--------------------------|-------------------------|----------------------|-----------------------------|----------------------|------------------|------------------|------------------|------------------|
| | | | | | | | | Before tocainide | During tocainide | Before tocainide | During tocainide |
| M | 63 | No | 12 | 1,800 | 8 | No | — | No | No | 4A | 3 |
| M | 57 | No | 32 | 1,800 | 8 | — | — | Yes | No | 4B | 1 |
| M | 5 | — | 9 | 1,800 | 8 | No | No | No | No | 4B | 4A |
| M | 41 | No | 23 | 1,200 | 8 | No | No | No | No | 4B | 2 |
| M | 66 | Yes | 0.3 | 2,400 | 8 | Yes | Yes | Yes | Yes | 4B | 4B |
| M | 44 | Yes | 42.5 | 3,000 | 6 | No | No | Yes | No | 4B | 3 |
| M | — | No | 2 | 1,200 | 8 | — | — | No | No | 4A | 1 |
| F | 57 | Yes | 0.3 | 1,800 | 8 | — | — | Yes | Yes | 4B | 4B |
| M | 64 | No | 3.5 | 1,800 | 8 | Yes | No | Yes | No | 4B | 1 |

Abbreviations: VA = ventricular aneurysm; ET = treadmill exercise testing; VEA = ventricular ectopic activity; VT = ventricular tachycardia

Table II Treatment before tocainide

| Drug | No of patients | Not effective | Contra indicated | Side effects |
|--------------|----------------|---------------|------------------|--------------|
| Quinidine | 9 | 9 | 0 | 2 |
| Tocainamide | — | 5 | 1 | 2 |
| D-c pyramide | 5 | 2 | 3 | 3 |
| Impranolo | 5 | — | 4 | 0 |
| Therapy | 3 | 3 | 0 | 0 |

effects intervened. After 48 hours of therapy an absorption distribution tocainide curve was obtained in every patient and thereafter trough level were used as a guide to therapeutic effectiveness. Peak levels which are achieved 60 to 90 minutes after the drug is taken were obtained if side effects occurred. The daily tocainide dose ranged from 1,200 to 3,200 mg/day (mean 1,900 mg/day) in the nine patients.

Prior to oral tocainide therapy, ventricular arrhythmias in all nine patients were documented during ambulatory coronary care unit or telemetry ECG monitoring. Subsequent short term (computerized arrhythmia detection system) and long term ECG ambulatory (Holter) monitoring was conducted at frequent intervals during tocainide therapy. In addition treadmill exercise testing (Bruce protocol) was employed in two patients in whom exercise testing had induced VEA/VT.

Ventricular arrhythmias were assessed by hourly counts of VEA and occurrence of couplets and VT during frequent outpatient ambulatory ECG monitoring. A reduction in VEA and elimination of couplets and/or VT was achieved during

treadmill exercise testing in the two patients with exercise induced VEA/VT.

Symptoms caused by VEA/VT were also monitored in all patients during oral tocainide therapy. Side effects were monitored through spontaneous comments and direct questioning at each visit. Prior to institution of tocainide therapy baseline ECGs, chest x-ray films, antinuclear antibody (ANA) titers, Coombs test and hematologic, hepatic and renal function were assessed. In addition urinalysis and ophthalmologic assessment were performed on all the patients. At periodic intervals throughout the duration of therapy these tests were repeated.

Results

Results are shown in Table I.

Arrhythmias. In three of five patients with VT there was either abolition or marked reduction in episodes of VT while they were on tocainide as assessed by 24 hour ambulatory monitoring (two patients) and by exercise testing (one patient).

In five of the nine patients there was a significant reduction in total hourly VEA count (4% VEA/hr before and 44 VEA/hr during tocainide therapy, $P < 0.05$, Student's t test). However in the group as a whole the mean hourly VEA before tocainide therapy was 362 ± 347 whereas during tocainide therapy it was 91 ± 137 ($P = 0.08$, Student's t test). In one patient there was an increase in mean hourly VEA count (13 to 60). When the Lown system of grading VEA was used for analysis there was an improvement in Lown grade of VEA in six of the nine patients. All nine patients were in Lown grade 4A or 4B prior to tocainide therapy. Three patients improved

pressure of 1 mm Hg (25%) in pulmonary artery diastolic pressure of 2 mm Hg (19%) in aortic diastolic pressure of 4 mm Hg (5%) and in systemic vascular resistance of 2 units (10%), there was a decrease in cardiac index of 0.2 L/min/m² (6%) and in stroke index of 3 ml/m. At 30 and 45 minutes there was a gradual return toward control values. Although correlated to the tocainide plasma concentrations the hemodynamic changes seemed to be more dependent upon the tocainide infusion rate as shown in Fig 2. During the tablet administration period no significant differences were observed at any time between the tocainide and placebo groups with respect to any of the hemodynamic variables measured.

Although some of the arrhythmias in the present study may have been artificially caused by the catheters a significant antiarrhythmic effect was seen during 1 hour after the tocainide infusion regarding ventricular tachycardia and multifocal and paired PVCs. In the four patients who had more than five PVCs per minute a reduction of the number of PVCs was seen in all. During the tocainide/placebo tablet period no significant difference was observed between the tocainide and placebo groups with respect to the incidence of ventricular arrhythmias. Most patients had minor side effects of little clinical importance. However three patients after the infusion had sudden onset of bradycardia and hypotension which were easily and rapidly treated.

Summary

The hemodynamic and antiarrhythmic effects were evaluated after tocainide was given intravenously over a 15 minute period to 18 patients with AMI within 24 hours after onset of symptoms. Doses were 0.5 (nine patients) and 0.75 (nine patients) mg/kg/min. Tocainide infusion produced small but statistically significant increases in heart rate, mean right atrial pressure, pulmonary artery diastolic pressure, aortic diastolic

pressure and systemic vascular resistance. It also caused small but significant decreases in cardiac index, stroke index and left ventricular stroke index. Although correlated to the tocainide plasma concentrations the hemodynamic changes seemed to be more dependent upon the tocainide infusion rate. The data from the present investigation suggest that an infusion rate of 0.50 mg/kg/min may be sufficient in patients with AMI. Ventricular tachycardia and multifocal and paired PVCs were significantly reduced after tocainide infusion. Most patients had side effects but these were mild and transient. After the tocainide infusion however three patients had an episode of bradycardia and hypotension which were easily and rapidly treated in all patients.

After the infusion the patients randomly and double blindly received either two 400 mg tocainide tablets or two placebo tablets and thereafter one tablet of either tocainide or placebo respectively every 8 hours for 24 hours. This resulted in plasma concentrations within the suggested therapeutic range, no significant hemodynamic changes and minor side effects. These findings suggest that oral tocainide can be used safely for antiarrhythmic therapy in patients with AMI.

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from Grade 4 to 1 two patients from Grade 4 to 3 and one patient from Grade 4 to 2 (Table I Fig 1) Three of five patients noted considerable improvement in palpitations

Pharmacokinetics The peak plasma tocamide levels in the nine patients ranged from 8.7 to 15.1 $\mu\text{g/ml}$ (mean 10.6 $\mu\text{g/ml}$) The trough tocamide levels ranged from 1.4 to 7.5 $\mu\text{g/ml}$ (mean 5.0 $\mu\text{g/ml}$) Higher trough (6.7 versus 4.0 $\mu\text{g/ml}$) and peak (12.7 versus 9.4 $\mu\text{g/ml}$) levels of tocamide were achieved in nonresponders compared to responders

Side effects Transient central nervous system (CNS) symptoms occurred in seven of the nine patients (77%) at some early point during tocamide therapy The most common symptoms were paresthesias (3 patients) ataxia (4 patients) blurring of vision (2 patients) and slurred speech (4 patients) Severe CNS side effects occurred in two patients on day 1 and day 3 of therapy (confusion and paranoia in one patient ataxia of gait and speech in the other) and precluded long term use of tocamide in these patients

Minor gastrointestinal side effects (nausea anorexia and vomiting) occurred transiently in six of the nine patients However both the gastrointestinal and CNS side effects were overcome in all nine patients by reduction of dosage or taking the drug with food

ANA titers were slightly elevated in three patients during tocamide therapy In one patient who previously developed procainamide induced lupus the ANA titers were markedly elevated prior to tocamide therapy In this individual ANA titers fell during tocamide therapy In two other patients minimally elevated ANA titers developed during long term tocamide therapy However neither of these patients has developed clinical evidence of lupus as yet The patient with procainamide induced lupus developed a skin rash on chronic tocamide therapy that did not recur on reinstitution of tocamide after initial withdrawal

No systemic (hepatic renal hematologic and ophthalmologic) abnormalities were detected during periodic blood tests during chronic tocamide therapy No significant ECG conduction abnormalities were detected during chronic tocamide therapy

Intravenous lidocaine responsiveness in the prediction of tocamide efficacy Intravenous lidocaine was used in eight of the nine patients for

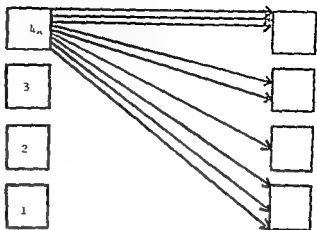


Fig 1 Improvement in Lown grade during tocamide therapy

suppression of VT/VEA prior to tocamide therapy Long term oral tocamide was effective in six of the eight lidocaine responders (75%)

Patients dying while on long term tocamide therapy Two patients died while on chronic tocamide therapy One of the two patients died from refractory cardiac failure 21 days following an extensive myocardial infarction and the second patient died from chronic congestive cardiac failure Neither of these deaths appeared to be related to tocamide therapy

Withdrawal of tocamide therapy Tocamide withdrawal was attempted in two responders after 28 and 19 months of chronic therapy respectively In both patients there was a prompt return of VEA during ambulatory monitoring in the first month following discontinuation of therapy No withdrawal was attempted in the three patients with VT who responded to and were on long term tocamide therapy

Discussion

Tocamide was effective in six of the nine (66%) patients for periods from 11 days to 42.5 months (mean 15.2 months) Four (41%) of these patients are still on maintenance tocamide therapy for periods of 3.5 to 42.5 months (mean 25.5 months) Three of the nine patients had a ventricular aneurysm and tocamide was effective in only one of these three patients In the majority of patients the drug was given every 8 hours and dosages ranged from 1,200 to 3,200 mg/day (mean 1,900 mg/day)

Minor side effects early on in therapy were

Prophylaxis of ventricular tachyarrhythmias with intravenous and oral tocainide in patients with and recovering from acute myocardial infarction

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In a double-blind placebo controlled study tocainide 750 mg i.v. during a 15 minute period directly followed by 800 mg orally and later 400 mg t.i.d. was administered to patients with acute myocardial infarction (AMI). Treatment was started as soon as possible following onset of symptoms. The follow up period was 6 months. The patient groups consisted of 56 tocainide and 56 placebo patients. There was no significant effect on the incidence of ventricular fibrillation or symptomatic ventricular tachycardia. The mortality rates were similar and low in both groups. Tocainide suppressed ventricular arrhythmias including ventricular tachycardia both in the acute stage of AMI and during convalescence. Tocainide also suppressed exercise induced ventricular arrhythmias. Side effects were in general mild or moderate.

Tocainide is an important new membrane active antiarrhythmic agent which we have evaluated in patients after myocardial infarction. The primary aim of this study was to assess the ability of tocainide to prevent ventricular fibrillation (VF), symptomatic ventricular tachycardia (VT) and sudden death in patients with acute myocardial infarction (AMI). Secondary aims were to assess the activity of tocainide against less serious spontaneous and exercise induced arrhythmias such as short runs of VT and ventricular premature complexes (VPCs) and to study the safety of intravenous and oral tocainide when given to patients with and recovering from AMI.

Material and methods

Patients The patients enrolled in the study were all admitted to the coronary care units (CCUs) of the Central Hospitals of Skovde and Helsingborg Sweden during the period from June 1978 to May 1979. All patients less than 74 years old and limited with symptoms suggestive of

AMI within the previous 48 hours were considered for inclusion. Indications for exclusion are summarized in Fig. 1.

Patients suitable for inclusion were then randomly treated with either tocainide or matching placebo. The dose of tocainide was 750 mg i.v. given by continuous infusion over a 15 minute period, 800 mg orally given at the end of the infusion and 400 mg orally given every 8 hours starting 8 hours later. Patients in the placebo group received intravenous saline solution followed by lactose tablets in an identical regimen. Treatment with oral medication was then continued double blind for a period of 6 months after the initial admission. Patients were withdrawn from the study if the diagnosis of AMI was not confirmed or if they developed defined exclusion criteria (Fig. 1).

Assessment procedures All patients included in the study were subject to standard CCU surveillance and treatment and following discharge they were assessed clinically at 1, 3 and 6 months.

Continuous ECG recordings were made by means of an Oxford instrument recorder for the first 24 hours in the hospital and following discharge) and at Skovde 1 and 6 months after

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experienced by the majority of patients (9 of 12 75%). However side effects were transient and overcome gradually by taking the drug with food or by dosage reduction. Side effects precluded long term therapy with tocainide in 2 of the 11 (18%) patients.

Intravenous lidocaine was effective in eight of the nine patients with myocardial infarction. Oral tocainide subsequently proved to be effective long term in six (75%) of these lidocaine responders.

No adverse conduction abnormalities were detected during this study. However none of the patients underwent intracardiac electrophysiology before or during tocainide therapy. Moore et al¹ have characterized the electrophysiologic safety of tocainide in man.

The effectiveness of tocainide in suppressing VEA/VT in man has previously been demonstrated in short term studies by Winkle et al³, Wosley et al⁴ and Ryan et al⁵ and in long term study by Winkle et al⁶ and Engler et al⁷. However in both of these long term studies, disopyramide was not employed prior to tocainide therapy. Moreover other antiarrhythmic medications were continued in their patients while on tocainide therapy.

We recognize the limitations of 24 hour and short term ambulatory ECG monitoring, the Lown grading system, the lack of a single accurate and reproducible standard for monitoring arrhythmias, and the lack of intracardiac VT initiation by pacing during tocainide therapy in our patients. However it appeared that in our highly symptomatic group of patients with VEA/VT resulting from chronic coronary artery disease, both symptomatic episodes of VT and VEA counts and complex forms decreased during tocainide therapy.

Tocainide appears to be a promising and useful addition to our limited armamentarium of antiarrhythmic agents. It would appear to be a logical choice for chronic therapy in those patients in whom lidocaine results in VEA/VT suppression. An acceptable level of side effects was noted early in therapy and no long term sequelae resulted from tocainide therapy in our patients.

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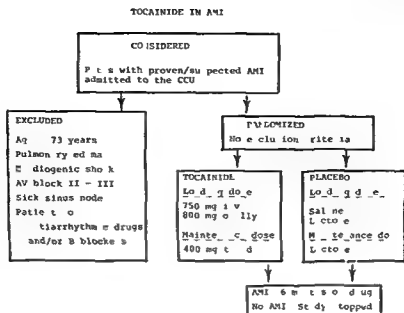


Fig 1 Study design

discharge. The patients from Skovde also had ECGs recorded during exercise testing on a bicycle ergometer conducted 1, 3 and 6 months after discharge.

Exercise tests were performed on an electrically braked bicycle ergometer (Siemens Elema, Sweden) under standardized conditions. The ECG was recorded at each work load reached and repeatedly during the first 10 minutes after exercise. The initial work load was usually 30 watts for women and 50 watts for men, which was then increased stepwise by 10 watts/min. For the exercise test 1 month following AMI, patients exercised either until definite symptoms occurred or until the increase in heart rate or other observations was such that it was thought prudent to stop. For the exercise tests at 3 and 6 months, all patients were exercised until symptoms such as angina pectoris, dyspnea, and tiredness made it impossible to continue work, serious ventricular tachyarrhythmias occurred (VT or numerous VPCs with hemodynamic deterioration) or a combination of these problems was noted. Thus the work load at 3 and 6 months may be considered maximal.

All 24-hour tapes were analyzed both by the use of a Pathfinder Arrhythmia Computer and by eye following operator-controlled printout of suspicious events. The number of hours containing no arrhythmias infrequent (< 30/hr) or frequent (> 30/hr) VPCs or VT (rate > 100 three or

more consecutive beats) and the number of patients with these arrhythmias in any assessment period was used for comparisons between the groups.

Exercise-induced ventricular tachyarrhythmias reported are arrhythmias occurring either during or directly following the exercise test and disappearing spontaneously with continued rest.

These VPCs have been classified as multifocal and paired and their frequency estimated at the time of occurrence.

Results

A total of 162 patients who fulfilled entry criteria were enrolled in the study. One other patient entered 55 hours after the onset of symptoms was excluded from the overall analysis. One hundred and twelve patients were diagnosed as having AMI by WHO criteria, and of these 56 were given tocainide and 56 placebo. In 50 patients the diagnosis of AMI could not be sustained. Twenty-six of these patients received tocainide and 24 placebo.

Because of technical difficulties it was not possible to analyze the tape recordings made in one of the centers (Helsingborg). Spontaneous ventricular arrhythmias not resulting in withdrawal from the study therefore are reported only for the patients enrolled at Skovde. Technical problems resulted in the loss of only a few tapes (~ 6%) and full 24-hour recordings were obtained

III Chronic tocainide therapy studies

A prospective randomized trial of tocainide in patients following myocardial infarction

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One hundred forty six patients with recent acute myocardial infarction were grouped at random into those treated with tocainide an oral analogue of lignocaine or placebo and followed up for 6 months in addition to standard investigations. A 24-hour ambulatory taped ECG recording was obtained prior to randomization and thereafter at 2, 8, 16 and 24 hours after discharge. The ECGs were analyzed by means of an automated computerized reporting system. Forty two patients had significant ventricular arrhythmias 10 of whom had effective plasma levels of tocainide compared with 27 patients on placebo ($P < 0.005$). In the placebo patients with increasing mobilization there was a consistent rise in the number of ventricular ectopic beats per day. There was no such increase in the tocainide patients ($P < 0.01$). Side effects were few and the incidence of central nervous system side effects was similar in both the tocainide and placebo groups. There was no conclusive evidence of myocardial depression, heart rate and blood pressure being unchanged over the 6 month period. Although ventricular arrhythmias were suppressed the number of patients in the study was too small to draw conclusions regarding the mortality rate.

The risk of sudden death is increased in patients with coronary heart disease particularly in patients with ventricular ectopic beats.^{1,2} It therefore seems reasonable to try and prevent such ventricular arrhythmias. Tocainide is an analogue of lignocaine and has been shown to be an effective antiarrhythmic agent in animals and in several preliminary studies in patients. It is almost 100% absorbed after oral administration and has a plasma half life of approximately 12 hours in patients with normal renal and hepatic function.^{3,4} The purpose of the present study was to evaluate the effects of tocainide on the prevention of ventricular arrhythmias in a placebo controlled trial in patients recovering from an acute myocardial infarction and followed up for a 6-month period. A further objective was to determine the incidence of side effects related to long term tocainide therapy.

MATERIAL AND METHODS

The patient population was drawn from three hospitals in Glasgow, Scotland (Dr D Ballantyne Victoria Infirmary and Dr W S Hillis Stobhill Hospital). The coordinating center was situated in the University Department of Medical Cardiology, The Royal Infirmary, Glasgow (Dr Ian Hutton). A total of 146 patients under the age of 70 years were entered into the trial. There were 121 men and 25 women with an average age of 55 years. The two groups were well matched with respect to age, site of infarction and estimated size of infarction from enzyme studies as can be seen in Table I. The diagnosis of acute myocardial infarction was confirmed clinically and by ECG changes—pathologic Q waves and sequential ST-T wave changes and by elevation of the serum enzymes serum glutamic oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH) and creatine phosphokinase (CPK).

Exclusion criteria were as follows: (1) abnormal renal or hepatic function, (2) Grade II or III A-V block, (3) persisting ventricular arrhythmias requiring treatment, (4) continued treatment

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Table 1 Characteristics of tocainide and placebo patients with AMI

| | Tocainide (n = 56) | Placebo (n = 56) | Difference |
|-----------------------------------|-----------------------|---------------------|------------|
| Sex | | | |
| Male | 48 | 41 | NS |
| Female | 8 | 15 | |
| Age (yr) | | | |
| Mean | 60 | 61 | NS |
| Range | 30-73 | 30-73 | |
| Previous AMI | | | |
| 0 | 48 | 49 | NS |
| 1 | 6 | 5 | |
| ≥ 2 | 2 | 2 | |
| Hypertension | 12 | 15 | NS |
| Diabetes | 8 | 5 | NS |
| Previous heart failure | 8 | 8 | NS |
| Angina < 1 mo | 17 | 17 | NS |
| Previous β blockade | 14 | 10 | NS |
| Delay onset of AMI to drug (hr) | | | |
| < 6 | 18 | 19 | NS |
| 6-24 | 28 | 19 | |
| > 24 | 8 | 15 | |
| Mean \pm SD | 13 \pm 10.2 | 16 \pm 13.0 | NS |
| Site of AMI | | | |
| Anterior | 28 | 20 | NS |
| Inferior | 22 | 22 | |
| Lateral | 2 | 3 | |
| Uncertain | 4 | 6 | |
| Maximal ST-segment elevation (mm) | | | |
| < 5 (0) | 38 | 40 | NS |
| 5-10 (0) | 15 | 11 | |
| > 10 (0) | 3 | 0 | |
| Mean \pm SD | 4.11 \pm 2.78 | 2.97 \pm 2.17 | $P < 0.05$ |
| Median | 3.38 | 2.49 | |

Ex: information not available for some patients (however < 24 for all).

in over 97% of the tapes available in this group. Therefore, the patient withdrawals account for the varying numbers of patients included in the arrhythmia analysis at different times. Contraindications to exercise testing in some patients contributed to a similar variation in the numbers of patients tested.

There were no significant differences between the groups in terms of sex distribution, age, past history, previous treatment, delay from onset of symptoms to inclusion and site of infarct. The maximum ST-segment elevation was not significantly higher in the group given tocainide (4.11 \pm 2.78 mm) as compared to the group given placebo (2.97 \pm 2.17 mm) ($P < 0.05$, Table 1).

Ten patients given tocainide and 10 given placebo

Table 2 Patients withdrawn from the study because of failure of therapy or potential side effects

| Reasons for withdrawal | Tocainide (n = 56) | Placebo (n = 56) | Difference |
|------------------------|-----------------------|---------------------|------------|
| Death | 11 | 5 | NS |
| VF | 3 | 7 | NS |
| VT | 2 | 2 | NS |
| Asystole > 4 s | 1 | 1 | NS |
| A-V block II | 1 | 1 | NS |
| Side effects | 9 | 2 | NS |
| Total | 22 | 17 | |

Table 3 Total number of patients with \geq 4 without frequent VPCs (> 30 /hr) and/or VT in the tocainide and placebo groups in any hour during a 24 hour ECG recording during the first 24 hours after 10 days and at 1 and 6 months

| Time period | Arrhythmia present | Tocainide | | Placebo | | Difference |
|-------------|--------------------|-----------|-----|---------|-----|------------|
| | | No | Yes | No | Yes | |
| 0-24 hr | Yes | 11 | 19 | 16 | 47 | $P < 0.05$ |
| | No | 20 | 81 | 18 | 51 | |
| 10 days | Yes | 2 | 11 | 2 | 10 | NS |
| | No | 20 | 91 | 18 | 40 | |
| 1 mo | Yes | 4 | 29 | 9 | 47 | NS |
| | No | 10 | 71 | 10 | 51 | |
| 6 mo | Yes | 1 | 8 | 8 | 41 | NS |
| | No | 11 | 92 | 10 | 50 | |

cebo were withdrawn at varying times during the first days of the study: some (nine) according to the protocol and some (11) because of their refusal to participate in the 6 month follow up phase of the study. Their withdrawal did not influence the comparability of the two treatment groups. Data derived from all patients with arrhythmia from the study are included in the appropriate analyses up to the time of withdrawal.

Deaths The mortality rate of the two groups was similar and the overall mortality in the study was low (8.7%). The mortality remained low (11.7%) when two patients who died after withdrawal from the study (one tocainide patient with aplastic anaemia, one placebo patient with VF) were included in the analyses.

Except for the patient with aplastic anaemia, none of the causes of death was unusual or unexpected in view of the primary diagnosis and none was unequivocally due to the administration of tocainide or the study design.

experienced by the majority of patients (9 of 12, 75%). However, side effects were transient and overcome gradually by taking the drug with food or by dosage reduction. Side effects precluded long term therapy with tocainide in 2 of the 11 (18%) patients.

Intravenous lidocaine was effective in eight of the nine patients with myocardial infarction. Oral tocainide subsequently proved to be effective long term in six (75%) of these lidocaine responders.

No adverse conduction abnormalities were detected during this study. However, none of the patients underwent intracardiac electrophysiology before or during tocainide therapy. Moon et al have characterized the electrophysiologic utility of tocainide in man.

The effectiveness of tocainide in suppressing V1A/V1 in man has previously been demonstrated in short term studies by Winkle et al,¹ Woodcock et al,² and Ryan et al,³ and in long term study by Winkle et al⁴ and Eagle et al.⁵ However in both of these long term studies,^{4,5} digoxin was not employed prior to tocainide therapy. Moreover, other antiarrhythmic medications were continued in their patients while on tocainide therapy.

We recognize the limitations of 24 hour and short term ambulatory ECG monitoring,⁶ the Lown grading system,⁷ the lack of a single sensitive and reproducible standard for monitoring arrhythmias, and the lack of intracardiac V1 stimulation by pacing during tocainide therapy in our patients. However it appeared that in our highly symptomatic group of patients with V1A/V1 resulting from chronic coronary artery disease, both symptomatic episodes of V1 and V1A counts and complex forms decreased during tocainide therapy.

Tocainide appears to be a promising and useful addition to our limited armamentarium of antiarrhythmic agents. It would appear to be a logical choice for chronic therapy in those patients in whom lidocaine results in V1A/V1 suppression. An acceptable level of side effects was noted early in therapy and no long term sequelae resulted from tocainide therapy in our patients.

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Table IV Frequency and type of VTs induced by exercise at 1, 3 and 6 months after AMI in patients given placebo

| Patient No | 1 mo (n = 21) | 3 mo (n = 19) | 6 mo (n = 19) |
|------------|---|--|--|
| 4 | 0 | 0 | 0 |
| 10 | — | 0 | 0 |
| 16 | 0 | Monofocal paired ~40/min (bigeminy) | Monofocal paired ~30/min (bigeminy) |
| 26 | Multifocal paired ~10/min | Multifocal ~30/min | Monofocal paired ~30/min (bigeminy) |
| 30 | Monofocal < 5/min | — | — |
| 36 | Monofocal paired ~50/min | VT repeated short bursts ~3 sec each | Monofocal ~15/min |
| 43 | 0 | 0 | 0 |
| 46 | 0 | 0 | 0 |
| 55 | Monofocal, paired ~60/min (bigeminy) | Monofocal paired ~40/min | Monofocal, ~20/min (bigeminy) |
| 56 | 0 | 0 | Monofocal < 5/min |
| 62 | 0 | Monofocal ~15/min | Monofocal ~70/min |
| 64 | Monofocal < 5/min | 0 | VT two bursts 25 sec each |
| 69 | 0 | 0 | Monofocal ~25/min |
| 73 | 0 | Monofocal < 5/min | 0 |
| 80 | 0 | 0 | 0 |
| 86 | 0 | 0 | 0 |
| 91 | Monofocal paired ~10/min | — | — |
| 92 | 0 | 0 | Monofocal < 5/min |
| 100 | 0 | 0 | 0 |
| 101 | 0 | 0 | 0 |
| 105 | Monofocal paired ~10/min | 0 | 0 |

Withdrawals Twenty two patients given tocinide and 13 given placebo were withdrawn from the study because of failure of therapy or potential side effects. The difference between the groups was primarily attributable to the greater number of patients withdrawn from tocinide because of side effects (nine compared to two). The number of patients withdrawn because of VT, asystole or A-V block was essentially the same in both groups (Table II).

Five patients in the tocinide group developed significant VT. One patient developed rapid VT 4 minutes after the start of the tocinide infusion and consequently had only a very low plasma level when withdrawn. Therefore the failure of tocinide therapy in this patient is questionable. However, the bursts of VT that were noted before the injection deteriorated into sustained rapid VT after tocinide. Although this is often the natural history of this arrhythmia, it is possible that the low concentration of tocinide produced a more rapid reentry circuit than was possible in the absence of the drug. Although the patient did not respond to procainamide, he did respond to disopyramide.

Two patients developed VF 45 hours and 11 days respectively after inclusion in the study. Plasma tocinide concentrations were low in both cases. Lidocaine was ineffective in both patients and the arrhythmias responded to procainamide. One patient developed VF despite having a plasma tocinide concentration in the middle of the suggested therapeutic range. This patient's arrhythmia was also refractory to lidocaine but responded to procainamide. One patient developed sustained VT at a rate of 180/min despite a therapeutic plasma tocinide concentration. The arrhythmia was also refractory to quinidine and procainamide. Since it was possible to terminate the arrhythmia repeatedly with intravenous lidocaine, the patient was again given tocinide but an increased dosage. This successfully controlled the arrhythmia.

Spontaneous VTs observed on continuous ECG recordings Over the first 24 hours continuous ECG recordings were obtained from 31 tocinide- and 34 placebo-treated patients. The total number of recorded hours was 1,291. The tocinide-treated patients had significantly fewer recorded hours containing VPCs than did the

III Chronic tocainide therapy studies

A prospective randomized trial of tocainide in patients following myocardial infarction

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One hundred forty six patients with recent acute myocardial infarction were grouped at random into those treated with tocainide an oral analogue of lignocaine or placebo and followed up for 6 months. In addition to standard investigations a 24-hour ambulatory taped ECG recording was obtained prior to randomization and thereafter at 2 8 16 and 24 hours after discharge. The ECGs were analyzed by means of an automated computerized reporting system. Forty two patients had significant ventricular arrhythmias 10 of whom had effective plasma levels of tocainide compared with 27 patients on placebo ($P < 0.005$). In the placebo patients with increasing mobilization there was a consistent rise in the number of ventricular ectopic beats per day. There was no such increase in the tocainide patients ($P < 0.01$). Side effects were few and the incidence of central nervous system side effects was similar in both the tocainide and placebo groups. There was no conclusive evidence of myocardial depression heart rate and blood pressure being unchanged over the 6 month period. Although ventricular arrhythmias were suppressed the number of patients in the study was too small to draw conclusions regarding the mortality rate.

The risk of sudden death is increased in patients with coronary heart disease particularly in patients with ventricular ectopic beats. It therefore seems reasonable to try and prevent such ventricular arrhythmias. Tocainide is an analogue of lignocaine and has been shown to be an effective antiarrhythmic agent in animals and in several preliminary studies in patients.¹⁻³ It is almost 100% absorbed after oral administration and has a plasma half life of approximately 12 hours in patients with normal renal and hepatic function.¹¹⁻¹² The purpose of the present study was to evaluate the effects of tocainide on the prevention of ventricular arrhythmias in a placebo controlled trial in patients recovering from an acute myocardial infarction and followed up for a 6-month period. A further objective was to determine the incidence of side effects related to long term tocainide therapy.

MATERIAL AND METHODS

The patient population was drawn from three hospitals in Glasgow Scotland (Dr D Ballantyne Victoria Infirmary and Dr W S Hillis Stobhill Hospital). The coordinating center was situated in the University Department of Medical Cardiology The Royal Infirmary Glasgow (Dr Ian Hutton). A total of 146 patients under the age of 70 years were entered into the trial. There were 121 men and 25 women with an average age of 55 years. The two groups were well matched with respect to age site of infarction and estimated size of infarction from enzyme studies as can be seen in Table 1. The diagnosis of acute myocardial infarction was confirmed clinically and by ECG changes—pathologic Q waves and sequential ST T wave changes and by elevation of the serum enzymes serum glutamic oxaloacetic transaminase (SGOT) lactic dehydrogenase (LDH) and creatine phosphokinase (CPK).

Exclusion criteria were as follows (1) abnormal renal or hepatic function (2) Grade II or III A V block (3) persisting ventricular arrhythmias requiring treatment (4) continued treatment

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Table V Frequency and type of VTs induced by exercise at 1, 3 and 6 months after AMI in patients given tocainide

| Patient No | 1 mo (n = 12) | 3 mo (n = 12) | 6 mo (n = 14) |
|------------|-------------------------------|----------------------|----------------------|
| 1 | — | — | 0 |
| 5 | 0 | 0 | 0 |
| 12 | 0 | Monofocal < 5/min | Monofocal < 5/min |
| | Multifocal paired ~ 10/min | | |
| 22 | 0 | 0 | 0 |
| 27 | 0 | 0 | 0 |
| 37 | 0 | 0 | — |
| 44 | 0 | 0 | 0 |
| 44 | 0 | 0 | 0 |
| 3 | — | 0 | 0 |
| 7 | 0 | 0 | 0 |
| 8 | 0 | 0 | 0 |
| 13 | 0 | 0 | — |
| 14 | 0 | 0 | 0 |
| 15 | 0 | 0 | 0 |
| 16 | 0 | 0 | 0 |
| 17 | 0 | 0 | 0 |
| 18 | 0 | 0 | 0 |
| 19 | 0 | 0 | 0 |
| 20 | 0 | 0 | 0 |
| 21 | 0 | 0 | 0 |
| 23 | 0 | 0 | 0 |
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| 100 | 0 | 0 | 0 |

placebo treated patients. Frequent VPCs and/or VTs on any occasion during the first 24 hours occurred in 19% of tocainide treated patients and in 4% of those given placebo. This difference is statistically significant ($P < 0.05$). The percent age of patients with VT was significantly greater in the placebo group (41% compared to 13%, $P < 0.05$).

One and six months after inclusion in the study, fewer patients in the tocainide group had VTs, but because of the small number of observations, this difference did not reach statistical significance (Table III). Notwithstanding this, the number of hours during which arrhythmias occurred was significantly less in the tocainide group at all assessment times except at 10 days.

Exercise induced ventricular arrhythmias. There were no significant differences between the maximum workload achieved by the two groups at any observation period, nor between the heart rates and systolic blood pressures. In general, the reasons for discontinuation of exercise were similar in the two groups. The development of VTs, however, resulted in discontinuation of the exercise test in three patients given placebo on four occasions, while in the tocainide group, exercise tests were discontinued because of development of such arrhythmias.

More patients in the placebo group developed VTs on exercise (Tables IV and V). Although the difference between the groups did not reach statistical significance at 1 and 3 months after AMI, the incidence of arrhythmic events in the placebo group was significantly greater at the 6 month exercise test ($P < 0.05$). A significantly greater number of patients in the placebo group had exercise arrhythmias on one or more occasions (13 compared to two, $P < 0.01$). Since VT did not occur after exercise in tocainide treated patients, the data suggest that tocainide was associated with a reduced incidence of serious ventricular arrhythmias in these patients. The greater number of patients with frequent paired and/or multifocal VPCs induced by exercise in the placebo group also supports this conclusion.

Tolerability. No clinically important changes in mean blood pressure or heart rate occurred within the 60 minute period following the injection of tocainide. There were no significant differences in mean blood pressure and heart rate between the tocainide and placebo treated groups 10 days, 1 month, 3 months and 6 months after the start of treatment. Side effects following intravenous injection were more common in the tocainide treated patients ($n = 17$) than in those receiving placebo ($n = 3$).

CNS symptoms were the most common side effects seen in the tocainide group and usually consisted of paresthesias described as a numbness in the throat, tingling sensations in the lips, a feeling of cold or warmth, and in a few cases, a tingling sensation in the arms. CNS side effects were all reported as mild or moderate except in one patient who developed confusion 5 minutes after the start of tocainide injection (250 mg). The infusion was stopped and the patient was withdrawn from the study. The symptoms disappeared completely 10 to 15 minutes after the injection was terminated.

Gastrointestinal complaints were the next most common side effects in patients given tocainide. These usually included mild to moderate nausea followed by vomiting.

Cardiovascular side effects occurred in four patients in association with intravenous tocainide administration and consisted of a fall in blood pressure and heart rate. The injection was completed when the blood pressure stabilized following atropine and/or a short break in the infusion.

Withdrawals due to side effects. Nine patients

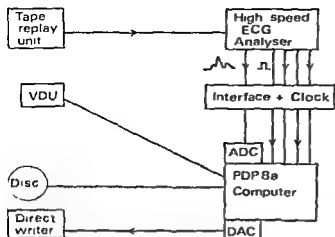


Fig 1 The tape replay computer analysis system ADC = analogue digital converter DAC = digital analogue converter VDU = visual display unit

with β adrenergic receptor blocking drugs and (5) persisting angina pectoris.

Patients were considered for entry into the study 7 to 10 days after hospital admission for acute myocardial infarction. The use of cardiac glycosides and diuretics was not considered a contraindication. A detailed history was obtained and physical examination performed. A 12 lead ECG and chest x ray film were taken. Blood was taken for standard hematologic and biochemical screening for hepatic and renal abnormalities and an antinuclear antibody (ANA) titer. A 24 hour taped ECG was recorded at a time when the patient was ambulatory prior to hospital discharge. Written consent was obtained from the patient and either tocainide 200 mg tid or placebo was given in a randomized double blind fashion. The patients were reviewed as outpatients at 2, 8, 16, and 24 weeks after discharge and again at 25 weeks when medication had been discontinued.

The preceding investigations including ANA and 24 hour ECG recording were repeated at each outpatient visit. In addition information regarding possible adverse events was carefully collected at each clinic visit. Blood was taken for plasma tocainide levels approximately 2 to 3 hours after administration of the medication.

Patients were withdrawn from the study if treatment failed i.e. if significant ventricular arrhythmias developed, and if an adverse event occurred such as left heart failure, angina pectoris requiring the use of β adrenergic receptor

Table 1 Clinical details of patient population

| Clinical data | Tocainide (n = 77) | Placebo (n = 71) |
|-------------------------------|----------------------------|----------------------------|
| Sex | 60 males 12 females | 61 males 13 females |
| Age (yr) | 57.6 ± 1 | 57.1 ± 1 |
| Site of myocardial infarction | Inferior 37 Anterior 30 | Inferior 40 Anterior 34 |
| Peak cardiac enzyme CPK (U/L) | 1360 ± 900 | 1133 ± 966 |

blocking drugs or side effects of such severity as to be unacceptable to the patient developed.

Twenty-four-hour ECG analysis ECGs were taped by means of Oxford Medical Instruments Medilog 24 hour recorders. The Oxford tape unit was linked to a high speed ECG analyzer (Pathfinder) of Reynolds Medical Electronics. A technician teaches the analyzer the morphology of the normal QRS complex and analysis thereafter is automatic once the appropriate triggering levels have been set. The outputs from the high speed analyzer are interfaced to a PDP8A minicomputer (Fig 1). The particular outputs utilized are the logic pulse which indicates whether a QRS complex is normal or abnormal. In addition the ECG signal itself is fed from the replay unit to the computer.

The interface has been designed to lengthen the logic pulse which indicated the morphology of the QRS complex. It also filters the ECG signal to remove high frequency noise. In addition it contains a clock used to control analogue to digital conversion of the ECG signal at a rate equivalent to 125 samples/sec real time. Arrhythmic events can be detected and automatically printed by the Pathfinder and/or by the computer. The printout from the computer provides a breakdown of the 24 hour recording into 15 minute periods for which the average heart rate and frequency of ventricular ectopic beats, supraventricular tachycardia and ventricular tachycardia are produced. Thus the system automatically captures arrhythmic events, produces an interpretation and outputs the relevant ECG strip.¹⁴

The accuracy of the reporting system is dependent on the Reynolds Pathfinder and this has been reported in a number of studies.¹⁴ The sensitivity of the method will depend on the population studied and for the identification of the aberrant beats the sensitivity is in the order

total were withdrawn from the tocainide study because of side effects. One patient suffered nausea and vomiting, two developed rashes, five had different types of CNS side effects, and one developed aplastic anemia. The gastrointestinal and in three cases the CNS side effects were finally considered to be caused by tocainide as were the rashes.

In one patient aplastic anemia was diagnosed 36 days after the start of treatment with tocainide. This patient had serious AMI resulting in congestive cardiac failure which was treated with furosemide, spironolactone, digoxin, and prazosin. The patient was readmitted with septicemia secondary to agranulocytosis. Tocainide and prazosin were withdrawn and the patient died of VF following the development of cardiogenic shock within 24 hours of admission. The etiology of the aplastic anemia is not known but tocainide, furosemide, spironolactone, and prazosin could be implicated as a cause of the aplastic anemia and agranulocytosis, although it is not possible to determine whether any of these agents singly or in combination were cause and effect related.

Plasma tocainide concentrations. The mean and individual plasma tocainide concentrations obtained in a random sample of patients from both treatment centers showed that the dosage regime produced mean plasma concentrations within the suggested therapeutic range (18 to 45 $\mu\text{mol/L}$) at all sampling times.

During the 6 month follow up period the vast majority of patients had tocainide concentrations within this range suggesting that compliance was good in general.

Discussion

Tocainide is a primary amine which in many respects is closely related to lidocaine.

However, in contrast to lidocaine, tocainide is rapidly and completely absorbed from the gastrointestinal tract and the first pass effect is negligible. In animal studies, tocainide has been found to be effective by both the intravenous and oral route for suppressing experimentally induced cardiac arrhythmias.^{1,2} Several studies of the efficacy of the drug in ventricular arrhythmias of varying origin have been carried out in humans. Winkle et al.³ found that serious chronic ventricular arrhythmias refractory to other antiarrhythmic agents could be controlled with tocainide in appropriate doses. The study also showed that there was a correlation between the concentra-

tion of the drug in plasma and the antiarrhythmic effect. Other investigators have reported similar results.⁴ These studies have mainly comprised patients with arrhythmias due to coronary heart disease and previous AMI. Experience with the use of tocainide for suppression of arrhythmias in the acute phase of myocardial infarction is still limited. Since the drug has been shown to have attractive electrophysiologic and hemodynamic qualities, it should possibly be advantageous to use it in patients with AMI, thereby combining the lidocaine-like characteristics with oral availability. In a study of the pharmacokinetic effects of tocainide on patients with AMI, it was shown that it was possible to achieve the results of Winkle et al.³ who suggested obtaining rapid therapeutic plasma concentrations by combining intravenous and oral administration. This plasma level was maintained during steady state conditions and the regimen did not induce any important untoward effects. It was therefore considered appropriate to perform a controlled investigation of the effects of tocainide in AMI.

In the present study, tocainide did not prevent VF, symptomatic VT, or sudden death in patients with AMI. Because of the small number of patients enrolled in the study and the surprisingly low overall mortality rate, it is not possible to conclude on statistical grounds that tocainide lacks the ability to prevent these events. Some of the patients who developed serious ventricular arrhythmias had low plasma tocainide concentrations at the time of the event and in one patient VT which occurred despite an apparently adequate plasma tocainide concentration was controlled by increasing the dosage. This suggests that it may be possible to improve arrhythmia control by increasing the dosage within the limits of patient tolerance. This is obviously not possible in a double blind study. The majority of patients achieved plasma tocainide concentrations in the range of 18 to 45 $\mu\text{mol/L}$, as was expected from our initial pharmacokinetic study of patients with AMI.⁵

The present study may indicate that the suggested therapeutic range is not generally valid but that higher concentrations are desirable in some patients. Individual titration of the tocainide dose until the highest level tolerated has been found might be preferable. Further studies involving a greater number of patients and individualized dosages are thus necessary to determine whether or not tocainide can prevent VF symp-

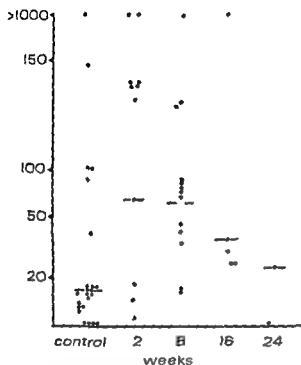


Fig 2 Number of ventricular ectopic beats found in 24 hours in placebo treated patients expressed on a log scale. The bars indicate the median value

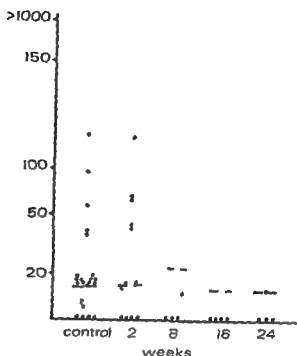


Fig 3 Number of ventricular ectopic beats found in 24 hours in tocainide treated patients expressed on a log scale. The bars indicate the median value

of 97%. The specificity however may appear to be exceptionally high if the number of false positive aberrant beats is related to the total number of beats in the 24 hour period. With the adoption of this form of analysis specificity may be regarded as high as 99.9%. The arrhythmias detected by the computer were initially analyzed and confirmed visually by two observers.

Plasma tocainide levels were estimated at Astra Clinical Research Center, Edinburgh. An effective plasma level of tocainide would appear to be $> 3 \text{ mg/ml}$.

Statistical analysis. The basic design was of a comparison between two treatments. Statistical analysis were a χ^2 test and Student's t test. A P value of < 0.05 was considered significant.

Results

Forty-two patients had significant ventricular arrhythmias and were withdrawn from the study. The plasma levels of tocainide in the patients receiving tocainide thus significantly

reduced the incidence of serious ventricular arrhythmias ($P < 0.005$).

There was considerable individual variation in the number of ventricular ectopic beats in any 24 hours. The range was 0 to 6547 ectopic beats in 24 hours. Consequently the results were expressed as the median number of ventricular ectopic beats per patient per day. In the placebo patients the median value on admission was 14 ventricular ectopic beats per patient per day and increased to 67 and 68 at 2 and 4 weeks respectively. This increase was maintained throughout the period of the study (Fig 2). In the tocainide patients there was no increase in the number of ventricular ectopic beats per patient. The median number of ventricular ectopic beats per patient on admission was 11 and there was little or no increase—12, 22, 9 and 9 (Fig 3). Thus tocainide produced a significant reduction in the number of ventricular ectopic beats found with increasing mobilization in these postmyocardial infarction patients treated with placebo ($P < 0.01$). The hemodynamic effects of tocainide can be seen in Fig 4. There was little or no change in systemic blood pressure or in heart rate throughout the 6

Table V Frequency and type of VTs induced by exercise at 1, 3 and 6 months after AMI in patients given tocainide

| Patient No | 1 mo (n = 13) | 3 mo (n = 15) | 6 mo (n = 14) |
|----------------|------------------------------------|----------------------|----------------------|
| 1 | — | — | 0 |
| 2 | 0 | 0 | 0 |
| 13 | 0 | 0 | 0 |
| | Multifocal, paired, ~10/min | Monofocal < 5/min | Monofocal < 5/min |
| 25 | 0 | 0 | 0 |
| 27 | 0 | 0 | 0 |
| 37 | 0 | 0 | — |
| 38 | 0 | 0 | 0 |
| 44 | 0 | 0 | 0 |
| 43 | — | 0 | 0 |
| 57 | 0 | 0 | 0 |
| 58 | 0 | 0 | 0 |
| 6 | 0 | 0 | — |
| 70 | 0 | 0 | 0 |
| 74 | 0 | 0 | 0 |
| — | Monofocal ~20/min (bigeminy) | 0 | 0 |
| N ₂ | 0 | 0 | 0 |

placebo-treated patients. Frequent VPCs and/or VTs on any occasion during the first 24 hours occurred in 19% of tocainide treated patients and in 4% of those given placebo. This difference is statistically significant ($P < 0.05$). The percentage of patients with VT was significantly greater in the placebo group (41% compared to 13% $P < 0.05$).

One and six months after inclusion in the study, fewer patients in the tocainide group had VTs, but because of the small number of observations, this difference did not reach statistical significance (Table III). Notwithstanding this, the number of hours during which arrhythmias occurred was significantly less in the tocainide group at all assessment times except at 10 days.

Exercise induced ventricular arrhythmias. There were no significant differences between the maximum work loads achieved by the two groups at any observation period, nor between the heart rates and systolic blood pressures. In general, the reasons for discontinuation of exercise were similar in the two groups. The development of VTs, however, resulted in discontinuation of the exercise test in three patients given placebo on four occasions, while in the tocainide group, no exercise tests were discontinued because of development of such arrhythmias.

More patients in the placebo group developed VTs on exercise (Tables IV and V). Although the difference between the groups did not reach statistical significance at 1 and 3 months after AMI, the incidence of arrhythmic events in the placebo group was significantly greater at the 6-month exercise test ($P < 0.05$). A significantly greater number of patients in the placebo group had exercise arrhythmias on one or more occasions (13 compared to two $P < 0.01$). Since VT did not occur after exercise in tocainide treated patients, the data suggest that tocainide was associated with a reduced incidence of serious ventricular arrhythmias in these patients. The greater number of patients with frequent paired and/or multifocal VPCs induced by exercise in the placebo group also supports this conclusion.

Tolerability. No clinically important changes in mean blood pressure or heart rate occurred within the 60 minute period following the injection of tocainide. There were no significant differences in mean blood pressure and heart rate between the tocainide and placebo treated groups 10 days, 1 month, 3 months and 6 months after the start of treatment. Side effects following intravenous injection were more common in the tocainide-treated patients ($n = 17$) than in those receiving placebo ($n = 3$).

CNS symptoms were the most common side effects seen in the tocainide group and usually consisted of paresthesias described as numbness in the throat, tingling sensations in the lips, a feeling of cold or warmth and in a few cases a tingling sensation in the arms. CNS side effects were all reported as mild or moderate except in one patient who developed confusion 5 minutes after the start of tocainide injection (2.0 mg). The infusion was stopped and the patient was withdrawn from the study. The symptoms disappeared completely 10 to 15 minutes after the injection was terminated.

Gastrointestinal complaints were the next most common side effects in patients given tocainide. These usually included mild to moderate nausea followed by vomiting.

Cardiovascular side effects occurred in four patients in association with intravenous tocainide administration and consisted of a fall in blood pressure and heart rate. The injection was completed when the blood pressure stabilized following atropine and/or a short break in the infusion.

Withdrawals due to side effects. Nine patients

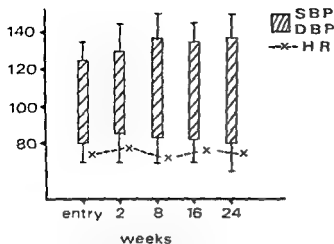


Fig 4 Effects of tocainide on systolic and diastolic blood pressure and heart rate. The results are expressed as the mean and the standard error of the mean.

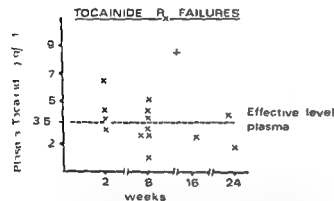


Fig 5 Plasma tocainide levels in patients who developed significant ventricular arrhythmias. Dotted line indicates that the effective plasma level of tocainide is greater than 3.5 µg/ml. + indicates sudden death in a patient.

months. Although this evidence is far from conclusive, tocainide would not appear to produce a significant depressant effect on the myocardium.

There was a high incidence of new cardiovascular events (15%) with four patients sustaining a further myocardial infarction and 18 patients developing angina pectoris of such severity as to justify the use of β adrenergic receptor blocking drugs.

Fifteen patients were withdrawn from the trial because of unacceptable side effects that were considered by the attending physician to be related to their medication. The detailed results are found in Tables II and III. It can be seen that the incidence of lightheadedness and hypotension

appeared to be higher in the tocainide treated patients. A severe skin rash appeared in 3 of the 71 patients treated with tocainide. There was a surprising similar incidence of central nervous system (CNS) symptoms in both treatment groups. These complaints consisted of paresthesia and twitching with no objective clinical evidence of CNS pathology. One patient developed allergic alveolitis while being treated with tocainide; the drug was discontinued with some improvement but only after corticosteroid therapy was begun, function restored to near normal with improvement in symptoms.

Neither significant ANA titers nor abnormal renal or hepatic function was found in any of the tocainide treated patients.

Patient compliance as assessed by tocainide blood levels was excellent. In three of the patients withdrawn from the study because of unacceptable side effects, with no objective evidence of pathology, there was little or no tocainide found in the plasma.

It is of interest that 7 of the 15 patients did not have effective plasma tocainide levels and significant ventricular arrhythmias were found in these patients. It is perhaps of greater interest that significant ventricular arrhythmias could still occur despite high plasma levels of tocainide (Fig 5). Indeed, sudden death occurred in a patient who had a plasma level of 9.1 µg/ml.

Discussion

This study has demonstrated that tocainide is an effective antiarrhythmic agent in patients followed up for 6 months after an acute myocardial infarction. The incidence of significant ventricular arrhythmias was reduced as was the increase in ventricular ectopic beats found in such patients known to have peptic ulceration or gastroesophageal reflux. There was no conclusive evidence of a depressant effect on the myocardium.

Adverse reactions, contraindications, lack of effectiveness, and frequent drug administration with established oral antiarrhythmic therapy have stimulated the search for additional orally effective antiarrhythmic drugs. In Europe amiodarone is used extensively and suppresses both supraventricular and ventricular arrhythmias. It is particularly effective in the treatment of tachyarrhythmias associated with the Wolff-Parkinson-White syndrome. The major side effect of

the transducer resolution still remains to be solved

More recently Silverman and associates¹ reported on the four chamber view in congenital heart diseases using an electronic sector scan. In addition Ports and associates¹¹ measured the displacement of the STL in Ebstein's anomaly with this method. It appears to be practical to utilize the apical cross section for the four chamber view according to their method when assessing the displacement of the STL from the right atrioventricular ring.

However this approach also has its limitations. In our experience we could not measure the displacement of the STL in the four chamber view in three out of the 11 patients in spite of the specific angiographic findings. In one of the three the STL was not identified from the four chamber view whereas the rudimentary STL was found in the three chamber view by angulating the transducer in the direction B from the cardiac apex (patient M T). In another of the three patients (T T) the four chamber view disclosed no displacement of the STL although it was measured as 1.5 cm at cardiac operation.

The downward displacement of the STL in our study was less than that reported by Ports and associates¹¹. This is probably attributable to the fact that there were milder forms of the anomaly in the majority of the patients examined. More over attention should be paid to the differentiation of the STL from the trabeculae in the right ventricle. The rudimentary STL should not be confused with other intracardiac structures. To separate the STL from other echo origins it is important to carefully observe the movement of each component of subvalvular structures using the cinematography or video system. Finally the downward displacement of the STL should be assessed in comparison with the findings at operation or autopsy in order to obtain the most appropriate cross section for the measurement.

With regard to the subxiphoid approach Chang and Feigenbaum¹ reported they could overcome the limitations of the standard techniques of M mode echocardiography. It is well known that the patient with emphysema or a large barrel chest is very difficult to examine with the transducer along the left sternal border.

Matsukubo and associates¹² applied this method to the measurement of the right ventricular wall thickness. Furthermore it has been extended

to the field of cross sectional echocardiography using electronic sector scanning¹³.

In Ebstein's anomaly the right sided heart chambers are extremely enlarged making it difficult to visualize the over all right ventricle from the apex to the base. In this connection the subxiphoid approach seems useful to observe the right ventricular apex to the base as well as the tricuspid subvalvular apparatus. However little has been reported on this and this is the reason we chose to undertake the present study.

In order to clearly describe the tricuspid subvalvular structures we adjusted the gain setting and deepened the focal point in comparison with standard cross sectional techniques. The interpretable images were available with the subxiphoid approach except for the patients with liver enlargement or tight abdominal wall. In contrast the displacement of the STL was detected by this technique only in three instances. Thus the four chamber view is thought superior to the subxiphoid approach in the detection of the distorted STL whereas the subxiphoid cross section is recommended when other approaches are not suitable to obtain intracardiac information.

Summary

Apex and subxiphoid cross sectional echocardiography was performed with an electronic sector scan on 11 patients having Ebstein's anomaly isolated or associated with other cardiac diseases. For control study 10 normal subjects and 10 ASD patients were similarly examined.

In the apical four chamber view the displacement of the STL was measured in end diastole using 11 mm cinematography. It ranged from 1.4 to 3.2 cm with an average of 2.1 ± 0.5 cm in eight out of the 11 patients whereas in control subjects there was no displacement of the STL.

From the apical three chamber view of the right side of the heart the downward displacement of the STL into the right ventricular cavity was also clearly visualized as well as the tricuspid valve ring. Thus the right sided heart was seen to be divided into the functional and atrialized right ventricles and the right atrium by the displacement of the STL.

In addition the CT inserting into the ATL was observed in five cases from the three chamber view and in four instances from the four chamber view.

The interpretable subxiphoid cross sectional

images were obtained in nine of the 11 patients. The right and left sides of the heart were widely visualized and the elongated ATL was fully observed from the tip to the thickened root. Moreover, the CT inserting into the ATL was visualized in six out of the nine patients.

We are grateful to Mr. Yoshihisa Kitamura for his technical assistance and to Mr. John M. Shields for correcting the English in this paper.

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Table II Side effects of therapy

| Side effects | Lightheadedness | Rash | Gastro-intestinal | Affect | CNS |
|--------------|-----------------|------|-------------------|--------|-----|
| Tocamide | 7 | 3 | 10 | 4 | 5 |
| Placebo | 2 | 0 | 6 | 2 | 5 |
| Withdrawal | | | | | |
| Tocamide | 2 | 2 | 2 | 0 | 2 |
| Placebo | 1 | 0 | 0 | 0 | 0 |

this compound is the finding of corneal deposits in nearly all of the patients. These deposits usually do not interfere with vision but may upset corneal metabolism.¹

Disopyramide is similar in its action to both quinidine and procainamide and like amiodarone is useful in the management of both supraventricular and ventricular arrhythmias. Anti-cholinergic side effects including dry mouth, blurred vision and urinary retention are not infrequent.¹ Significant myocardial depression in patients with left ventricular dysfunction has recently been reported by Podrod et al.

Mexiletine has similar electrophysiologic properties to lignocaine and thus is useful in the management of ventricular arrhythmias. Chamberlain has recently reported that mexiletine effectively suppressed ventricular arrhythmias in a group of postmyocardial infarction patients without however influencing the mortality rate. A number of side effects have been reported consisting either of gastrointestinal problems such as nausea and vomiting or CNS problems with tremor, ataxia and paresthesia.

Tocamide would appear to be effective and to have relatively few side effects in a dosage of 400 mg tid. It is of interest that there were a considerable number of nonspecific side effects related to placebo therapy in this postmyocardial infarction group of patients. CNS side effects might be anticipated with this analogue of lignocaine but in the dosage used in this study there was no objective evidence of CNS pathology despite complaints of lightheadedness, tremor and paresthesia in some patients. The similar incidence of CNS symptoms in the placebo group of patients emphasizes the need for caution in relating side effects to any form of drug therapy.

It was noted that significant ventricular arrhythmias could occur despite adequate circulating levels of tocanide. The particular assay

Table III Side effects of therapy

| Side effects | Malaise | Allergic lung disease | Insomnia | Polymyalgia |
|--------------|---------|-----------------------|----------|-------------|
| Tocamide | 0 | 1 | 2 | 0 |
| Placebo | 2 | 0 | 2 | 1 |
| Withdrawal | | | | |
| Tocamide | 0 | 1 | 1 | 0 |
| Placebo | 1 | 0 | 0 | 1 |

used for the estimation of plasma levels was different from that used by other workers and the effective plasma level of tocanide in this study would appear to be a level greater than 3.5 µg/ml. Winkle et al.⁸ have previously reported that tocanide was successful in controlling ventricular arrhythmias in 53% of patients proving unresponsive to quinidine, procainamide or propranolol. As in this study, significant ventricular arrhythmias and sudden death could still occur despite more than adequate circulating blood levels of tocanide.

These results suggest that tocanide is a safe and effective antiarrhythmic agent in postmyocardial infarction patients but a larger number of patients is required before we can conclude that a reduction in ventricular arrhythmias is associated with a reduced mortality rate.

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Tocainide for drug resistant ventricular arrhythmias Efficacy, side effects, and lidocaine responsiveness for predicting tocainide success

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Tocainide therapy has been evaluated in 38 patients with ventricular arrhythmias. Thirty-one had recurrent sustained ventricular tachycardia and/or fibrillation and 29 required prior cardioversions. These arrhythmias could not be managed with quinidine, procainamide, disopyramide, or propranolol. Tocainide doses averaged 1,500 mg/day (range 600 to 2,400) and the majority of patients had plasma concentrations from 6 to 12 µg/ml. Twenty-two patients (61%) had their arrhythmias controlled with tocainide and 16 (39%) did not. Tocainide dose and plasma concentrations were similar for responders and nonresponders. Lidocaine was effective in 26 patients and 16 (63%) of these had their arrhythmias controlled with tocainide. Of 12 patients in whom lidocaine was known to be ineffective or who had not been previously treated, only two (17%) had arrhythmias controlled with tocainide ($P < 0.02$). Side effects occurred in approximately two thirds of patients but required discontinuation of long-term tocainide in only three patients.

Tocainide is a lidocaine analogue that is effective for treating ventricular arrhythmias. It has nearly complete bioavailability and a plasma half-life averaging 13.5 hours. Plasma concentration is directly proportional to dose in individual patients and there is a narrow range of intersubject variation of plasma concentration for any dose. Electrophysiologically, tocainide resembles lidocaine, and its primary hemodynamic effect after intravenous dosing is a modest elevation of vascular resistance resulting in a slight rise in arterial pressure.

This study reports our experience with the use of long-term tocainide in a group of patients with severe ventricular arrhythmias that could not be managed with other generally available antiarrhythmic drugs. We will examine the efficacy and side effects and the value of lidocaine responsiveness for predicting arrhythmia control with tocainide.

ness for predicting arrhythmia control with tocainide

Methods

Thirty-eight patients with ventricular arrhythmias are the subjects of this report. This report includes and provides further follow-up on the 17 patients reported on in 1978.¹ Each patient had ventricular arrhythmias that could not be managed adequately with currently available antiarrhythmic drugs. All gave written informed consent and the therapy was approved by the Stanford Human Subjects Committee.

For patients with frequent recurrent episodes of sustained ventricular tachycardia or ventricular fibrillation, tocainide therapy was considered successful when control of these severe occurrences was established. For patients with ventricular ectopic activity, tocainide was considered successful when there was nearly complete elimination of ventricular ectopic beats.

Initial dosing with tocainide was undertaken for most patients at 400 mg every 6 hours. The

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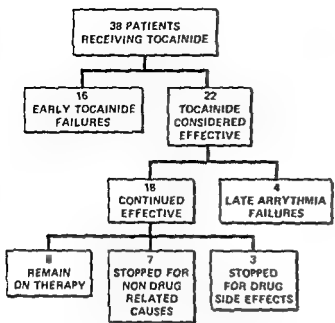


Fig 1 Outcome in 38 patients with ventricular arrhythmias treated with tocainide

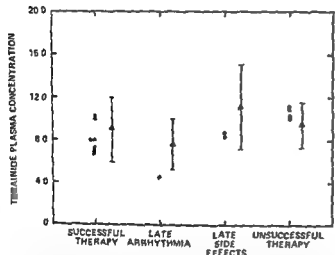


Fig 2 Mean tocainide plasma concentration over one dosing interval. Most patients plasma concentrations were between 8 and 12 µg/ml. There was no significant difference between the plasma concentrations in those treated successfully and those treated unsuccessfully.

dosage was gradually increased until arrhythmias were controlled or side effects occurred. Frequent blood sampling was performed and plasma concentrations given for each patient represent an estimate of the average over a dosing interval. For each patient assessment was made as to the responsiveness of the arrhythmias to lidocaine. Comparison between the success or failure of tocainide in patients responsive or nonrespon-

Table 1 Response to lidocaine for predicting tocainide success

| Tocainide | Lidocaine effective | Lidocaine ineffective | Lidocaine not evaluated |
|--------------------|---------------------|-----------------------|-------------------------|
| Effective | 16 | 1 | 1 |
| Ineffective | 10 | 3 | 7 |
| No effective/total | 16/26 (63%) | 1/4 (2%) | 1/8 (1%) |

sive to lidocaine was performed by means of the Fisher exact test.

Results

Patient population There were 38 patients (23 male 15 female) receiving tocainide; the average age was 58 ± 12 years. Twenty one had coronary disease, seven had prior valve replacement, four had mitral valve prolapse, three had a cardiomyopathy, and three had an otherwise normal heart. Congestive heart failure played a prominent role in the prior clinical course of 16 patients.

The arrhythmia was sustained ventricular tachycardia and/or fibrillation requiring pharmacologic or electrical conversion in 31 patients. Twenty eight patients had experienced more than one episode and 29 had a prior cardioversion. In seven patients the arrhythmia was symptomatic ventricular ectopy.

Thirty six patients had been treated unsuccessfully with quinidine (average daily dose of 15 ± 0.44 gm), 13 with procainamide (2.9 ± 1.1 gm), 28 with propranolol (140 ± 101 mg) and 11 with disopyramide (675 ± 324 mg).

Results of tocainide therapy The results of tocainide therapy are shown in Fig 1. Tocainide therapy was initially effective in 22 of the 38 patients (61%). Four had late arrhythmia recurrences, including two who died of ventricular fibrillation after 3½ and 4 months of therapy. Eighteen patients had their arrhythmias treated continuously and successfully with tocainide. Three of these required discontinuation of the drug after 6, 7, and 27 months because of side effects (see below). The remaining 15 patients were treated successfully with tocainide (median duration 13 months). Eight remain on tocainide and in seven it was discontinued for nondrug related causes (One had a spontaneous decline in arrhythmias, two died after coronary bypass sur-

Open clinical studies at a referral center

Chronic maintenance tocainide therapy in patients with recurrent sustained ventricular tachycardia refractory to conventional antiarrhythmic agents

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Chronic maintenance tocainide therapy was effective in controlling symptomatic recurrent ventricular tachycardia in 11 of 15 patients. Patients were selected for tocainide therapy on the basis of refractoriness to conventional antiarrhythmic agents and responsiveness to the intravenous administration of lidocaine. Side effects were frequent but could usually be managed by taking the drug with meals or by more frequent administration of smaller doses. Survival frequency of symptomatic tachycardia, frequency of asymptomatic ventricular tachycardia, and tolerance of the therapeutically effective dosage were the criteria used to assess therapeutic effectiveness. Factors common to the response group included primary and secondary QT prolongation before therapy, a paradoxical increase in ventricular ectopic activity with quinidine-like medications, and shortening of the QT interval with maintenance tocainide therapy. These factors may prove to be useful in identifying the patients who are most likely to benefit from chronic maintenance tocainide therapy.

During the last 400 years the science of medicine has evolved through the use of descriptive analysis, experimental investigation, modern mathematics, and technologic advances. The value of descriptive analysis is exemplified by Withering's report in 1785¹ on the use of foxglove (*Digitalis purpurea*). In the report his observations of 10 years on drug preparation, dose effect, and adverse reactions were analyzed. Withering cautioned his readers that "no general deductions decisive upon the failure or success of the medicine can be drawn from the cases I now present." I wish the reader to keep in view that it is not my intention merely to introduce a new diuretic to his acquaintance, but one which

though not infallible, I believe to be [of] use. After all, in spite of opinion, prejudice, or error, TIME will fix the real value upon this discovery.

The importance of these clinical observations persists today. The reasons for initiating therapeutic trials are to confirm the useful properties of a drug, device, or procedure; to define the adverse side effects; and to provide a potentially effective intervention for patients with disabling conditions that are refractory to all available therapy.² In keeping with these goals, our experience with tocainide, a lidocaine analogue obtained through an emergency open clinical study for patients with refractory ventricular tachycardia, is presented.

Selection of patients

From June 1977 to April 1980, seventy-eight patients hospitalized at our institution with symptomatic recurrent ventricular tachycardia

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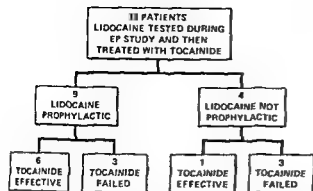


Fig 3 Outcome in 13 patients in whom lidocaine was tested for protection against ventricular tachycardia induced during intracardiac electrophysiologic study. Although the acute response to lidocaine was fairly predictive of the long term success or failure of tocainide, the correlation was imperfect.

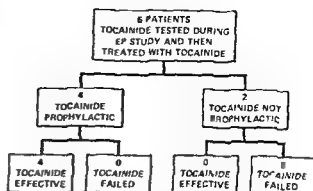


Fig 4 Outcome in six patients undergoing a repeat electrophysiologic study to evaluate ventricular tachycardia inducibility on oral tocainide. Although the number of patients is small, there was a perfect correlation between the outcome of the electrophysiologic study and long term therapy.

ger) was performed for angina, one died of lung carcinoma, and three died of heart failure.)

Sixteen patients failed to have their arrhythmia controlled with tocainide despite maximally tolerated doses of tocainide. The median duration of treatment in these patients was 7 days.

Dose and plasma concentration. The total daily dose of tocainide ranged from 600 to 2,400 mg daily. There was no difference between the daily dose of those treated effectively ($1,528 \pm 379$ mg/day) as compared to those treated ineffectively ($1,514 \pm 412$ mg/day). There was no difference between the plasma concentration for those responding to tocainide (8.9 ± 3.1 µg/ml) and those not responding (9.4 ± 2.2 µg/ml) (Fig 2).

Lidocaine responsiveness for predicting tocainide success. Since many of these patients were referred because their arrhythmia was responsive to lidocaine, we evaluated the value of a good lidocaine response for predicting the success of tocainide. Table I summarizes the results. Tocainide therapy was successful in 63% of patients in whom lidocaine was considered effective. Tocainide was successful in only two (17%) of the other 12 patients in whom lidocaine was ineffective or in whom it was not evaluated. The difference between these groups is statistically significant ($P < 0.02$).

There were 13 patients in whom lidocaine was tested during an electrophysiologic study (Fig 3). Lidocaine protected against induced ventricular tachycardia in 9 of these 13. Six of these nine had successful oral tocainide therapy. Lidocaine did

not protect against ventricular tachycardia in four patients. In three of these patients, tocainide therapy was a failure. Of six patients in whom oral tocainide was tested during a second electrophysiologic study (Fig 4), four were treated successfully. Both patients for whom tocainide was not prophylactic at the time of electrophysiologic study had subsequent spontaneous recurrences of ventricular arrhythmias. Lidocaine responsiveness during the electrophysiologic study may aid in selecting patients for oral tocainide therapy. However, all patients should be retested with tocainide prior to hospital discharge.

Side effects. Two thirds of patients had side effects (Table II). Side effects occurring during chronic oral therapy tended to be infrequent and were usually not a serious limitation to tocainide therapy. Tremor was minimized by taking the drug with food.

Three patients had severe side effects during long term therapy and required discontinuation of tocainide. One had a prior history of idiopathic and procainamide induced pericarditis. Tocainide was stopped after 7 months because of anemia, fever, and pericarditis. Another developed severe arthralgias and arthritis involving the hands after 4 months of therapy, which resolved when tocainide was discontinued. There was a slight rise in the antinuclear antibody titer. This patient had undergone a brief treatment with procainamide 2 months earlier. The third patient had an immunologic side effect that seemed best attributed to tocainide. After 27 months, the patient presented with gross hematuria and had a rise in creatinine

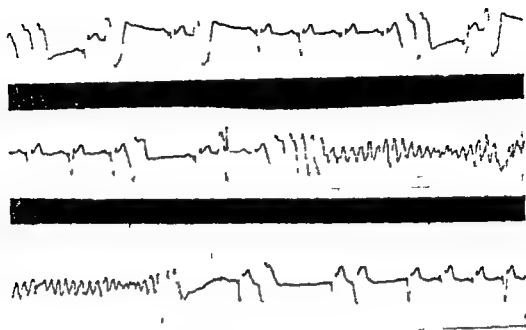


Fig 1 Case 1 Continuous monitoring strip recording of ventricular flutter occurring after second open heart surgery and use of quinidine sulfate

refractory or intolerant to conventional therapy (quinidine procainamide disopyramide propranolol and digitalis—alone or in combination) entered open clinical trials of investigational drugs devices or procedures. Seventeen of these patients were managed with cardiac surgical procedures guided by epicardial and intramural electrophysiologic mapping techniques.³ Nine patients received investigational pacing devices for burst ventricular overdrive conversion⁴ or dual chamber atrioventricular sequential pacing for control and prevention of ventricular tachycardia associated with intermittent symptomatic bradycardia. Fifty seven patients participated in open clinical drug trials of mexiletine verapamil aprindine or tocainide.⁵ Assignment of an individual patient to a specific drug trial was determined on the basis of the underlying myocardial disease the electrophysiologic characteristics of the tachycardia and the clinical judgment of the attending physician. Five patients participated in more than one of the clinical trials. Fifteen patients entered the tocainide drug trial and provide the data for this report.

Material and methods

Definitions. An open clinical study (trial)⁶ is defined as a clinical experiment with an investiga-

tional drug device or procedure which is applied to achieve a specific outcome and which is known to the patient and to the physician. A control or comparison group attained through randomization techniques and the administration of placebo agents are excluded.

Ventricular tachycardia is paroxysmal wide complex tachycardia that fulfills the standard electrocardiographic or electrophysiologic (or both) criteria.⁷

Chronic recurrent ventricular tachycardia is symptomatic ventricular tachycardia that is documented two or more times and occurs in the absence of an acutely evolving process such as recent myocardial infarction.

Sustained paroxysmal ventricular tachycardia is tachycardia lasting for more than 30 seconds or requiring emergency treatment because of hemodynamic collapse or progression to ventricular fibrillation.

*Torsade de pointes*⁸ is a variant of rapid ventricular tachycardia which has a surface ECG pattern characterized as a screwlike pattern (rhythmically changing polarity of the QRS deflection as if the sequence of depolarization were turning about the point).

Q-T prolongation^{9,10} is defined as Q-T and Q-T intervals obtained from the standard elec-

Table II Tocainide side effects

| Side effects | Dose finding (N = 32) | Chronic therapy (N = 24) |
|-------------------------|--------------------------|--------------------------------|
| Tremor | 16 (49%) | 10 (42%) |
| Nausea | 9 (28%) | 1 (4%) |
| Anxiety | 3 (8%) | 0 (0%) |
| Rash | 2 (5%) | 1 (4%) |
| Dizziness | 2 (5%) | 0 (0%) |
| Decreased mental status | 2 (5%) | 0 (0%) |
| Diaphoresis | 1 (3%) | 3 (12%) |
| Ataxia | 1 (3%) | 3 (12%) |
| Lightheadedness | 1 (3%) | 1 (4%) |
| Menthol on lips | 1 (3%) | 0 (0%) |
| Nystagmus | 1 (3%) | 0 (0%) |
| Increased arrhythmias | 1 (3%) | 0 (0%) |
| Visual problems | 1 (3%) | 1 (4%) |
| Fatigue | 1 (3%) | 0 (0%) |
| Constipation | 0 (0%) | 1 (4%) |
| Hot and cold flashes | 0 (0%) | 3 (12%) |
| Nightmares | 0 (0%) | 1 (4%) |
| Pericarditis | 0 (0%) | 1 (4%) |
| Arthritis | 0 (0%) | 1 (4%) |
| Glomerulonephritis | 0 (0%) | 1 (4%) |

to 27 mg/dl. A renal biopsy showed an immune complex glomerulonephritis. This was a nonmembranous glomerulonephritis with immune complex deposition in both the mesangium and the basement membranes. Immunofluorescent staining was positive for IgG, IgM, IgA, and C3 was deposited in a granular pattern (Fig 5). There was no rise in antinuclear antibody titers and antibodies to native DNA were negative. With withdrawal from tocainide resulted in a gradual improvement in renal status.

Discussion

This report summarizes our experience with tocainide in a group of patients with severe and life threatening ventricular arrhythmias difficult to manage with standard antiarrhythmic drugs. Conclusions from such studies must be made with caution. It is difficult to standardize therapy and to make carefully controlled observations with regard to efficacy and side effects. Nonetheless, our data suggest that tocainide is a valuable antiarrhythmic drug for the management of such patients.

This study suggests a reasonable correlation between responsiveness to lidocaine and successful outcome of tocainide therapy. An important unanswered question is the tocainide response

rate of patients not preselected because of lidocaine responsiveness. Only one of eight patients in whom the lidocaine responsiveness status was unknown responded to tocainide. In our study, the apparent success of tocainide may in large part be due to the fact that patients were preselected because of their lidocaine responsiveness. Nonetheless, the availability of oral tocainide for patients responsive to lidocaine does represent a valuable addition to our list of antiarrhythmic drugs.

Our data suggest that testing intravenous lidocaine in the electrophysiology laboratory¹ can be of value for selecting patients who have a high likelihood of arrhythmia control with tocainide. All patients who respond to lidocaine in the electrophysiology laboratory should undergo subsequent electrophysiologic testing on oral tocainide.

The range of plasma concentrations associated with excellent arrhythmia control for tocainide was generally from 6 to 12 µg/ml. The plasma concentrations associated with side effects were probably only marginally higher than the therapeutic range since many patients were treated with doses just below those associated with side effects. For most patients the dose was 400, 500, or 600 mg every 8 hours. The doses and plasma concentrations for those patients failing tocainide were in the same range as those in patients who had a good response. In this study, drug plasma concentrations were measured only in retrospect and did not play any role in the management of the patients. For these critically ill patients we preferred to increase the tocainide dose to the point where side effects developed and then diminish it slightly. Such a practice is reasonable with tocainide since the side effects occur when patients are under careful observation, are minor and resolve promptly, and there seems to be little danger of creating serious conduction disturbances or potentially lethal arrhythmias.

Although side effects occurred in two thirds of the patients, they required drug discontinuation in less than 10% of patients. The commonest side effect was a slight tremor, most often noted in the upper extremities. Nausea was the second most common side effect. The three patients requiring discontinuation during long term therapy all experienced immunologic side effects. In two of the three it was not certain that tocainide was the

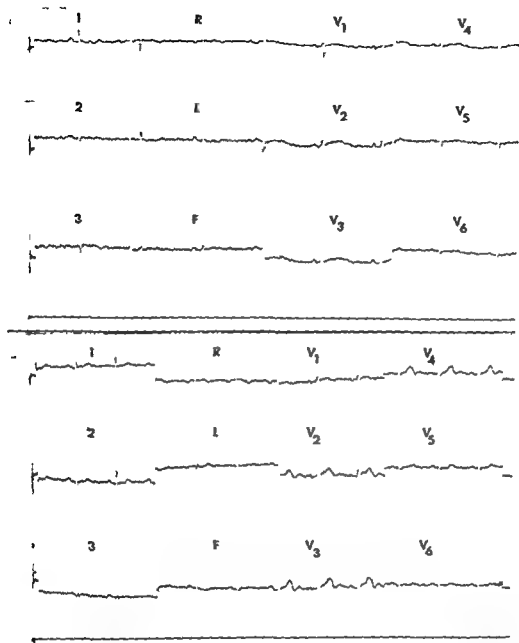


Fig 2 Case 10 Top Electrocardiogram recorded 8 days after cardiac arrest (April 8 1978) Pronounced repolarization abnormalities and prolonged Q T intervals are present Bottom Electrocardiogram recorded while patient was receiving 2400 mg tocainide/day (May 9 1978) Repolarization abnormalities and prolonged Q T intervals have improved

trocardiograms and vectorcardiograms which are 10 msec or more beyond the upper limits of normal for age sex and cycle length

Quinidine like medications include quinidine procainamide and disopyramide—antiarrhythmic agents that have membrane stabilizing properties combined with prolongation of the action potential duration

Protocol design and entry criteria All patients entering the emergency open clinical study were hospitalized at our institution for the diagnosis and treatment of recurrent symptomatic ventricular tachycardia or ventricular fibrillation and associated heart disease All but two of the patients were referred from other medical facilities because of therapeutic unresponsiveness The

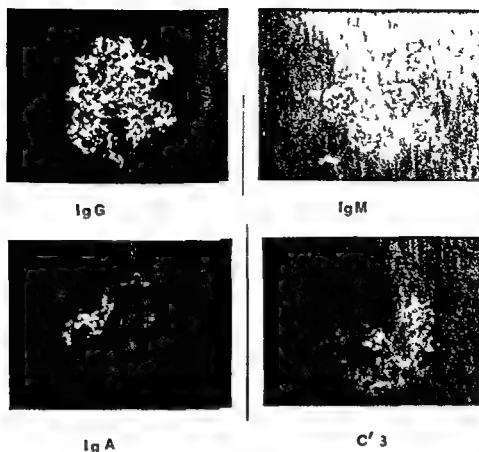


Fig 5 Immunofluorescent stains from renal biopsy of the patient who developed glomerulonephritis. There is an irregular lumpy bumpy pattern of immune complex deposition in the glomerulus.

precipitating factor. One patient had immune complex glomerulonephritis without a rise in the antinuclear antibody titer suggesting that the antibodies formed may not cross react with nuclear proteins.

One potential advantage of tocainide may be its minimal arrhythmogenic potential. Although one patient in our series may have had ventricular irritability increased by tocainide, the drug seemed remarkably free of aggravation of serious arrhythmias. Tocainide slightly diminishes the right ventricular effective refractory period and has no significant effect on Q-T interval. It would not be expected to cause the usual type of drug-induced *torsade de pointe*. Although many of our patients had severe heart failure, the drug was well tolerated. However, the hemodynamic effects of tocainide after oral therapy have not been well studied and the drug should be used with caution in patients with uncontrolled heart failure. We did not observe worsening of conduc-

tion disturbances, but caution should be exercised in patients with severe conduction abnormalities.

In summary, tocainide is a useful addition to the group of drugs available to treat severe refractory ventricular arrhythmias. We had a reasonable success rate in a group of patients predominantly selected for tocainide because of known responsiveness to lidocaine. Further studies will be required to evaluate the drug's effect in less critically ill patients, in patients not necessarily responsive to lidocaine, and in those who have been treated successfully with other antiarrhythmic drugs. The drug requires careful individual patient titration to achieve optimal antiarrhythmic effect and to minimize the occurrence of side effects. Most side effects are mild and respond to minor dose adjustments. Occasionally the drug must be discontinued because of immunologic side effects during long-term therapy.

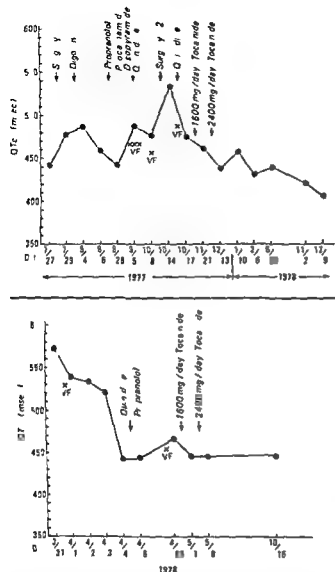


Fig 3 Time course change in corrected QT intervals. QT intervals were computed from Bazett's formula $QT = QT_c \cdot \sqrt{RR}$. Top Case 1 QT intervals remained near normal during 1979 and 1980 and the patient has been free of recurrent ventricular tachycardia-ventricular fibrillation. Bottom Case 10 QT intervals have remained in normal range throughout 1979 and 1980 and the patient has been free of ventricular tachycardia-ventricular fibrillation.

diagnosis of symptomatic refractory recurrent sustained ventricular tachycardia was accepted when (1) ECG or intracardiac electrophysiologic (or both) recordings confirmed the arrhythmia diagnosis and (2) near maximal amounts of commonly available antiarrhythmic agents alone or in combination were unsuccessful in preventing spontaneously occurring sustained ventricular tachycardia or ventricular fibrillation. Plasma drug levels were used for determining unresponsiveness and patient compliance. If the clinical

history, referral hospital records or plasma drug levels corroborated unresponsiveness or intolerance the same therapeutic trial was not routinely repeated. When the arrhythmia diagnosis was uncertain and the response to a specific antiarrhythmic therapy difficult to assess. His bundle recordings combined with programmed ventricular stimulation or other provocative testing techniques were used to evaluate the patient's status. Serial ventricular stimulation studies were used to assess the therapeutic effectiveness in those patients with reliably induced and terminate ventricular tachycardia.¹³

Refractoriness to conventional antiarrhythmic agents combined with responsiveness to intravenously administered lidocaine was required of each patient before entry into the clinical trial. All participants were informed of the experimental nature of tocainide and gave written consent prior to entry. The therapeutic goals for each patient were predefined and included (1) survival, (2) prevention of recurrent sustained ventricular tachycardia and associated hemodynamic collapse, (3) prevention of spontaneously occurring sustained and nonsustained ventricular tachycardia and (4) attainment of a satisfactory balance between control of ventricular tachycardia and unacceptable adverse reactions to tocainide.

Results

Characteristics of patients All 15 patients had well documented recurrent ventricular tachycardia before entering the open clinical trial. The duration of symptoms before referral ranged from 2 months to 11 years. The ages of the 15 patients (10 males and 5 females) ranged from 9 to 61 years. Oral tocainide therapy was maintained from 4 days to 34 months. All patients who were responsive and tolerant to tocainide were on chronic maintenance therapy for more than 6 months. Eleven of the 15 patients continued on chronic maintenance therapy. Five patients have been withdrawn from the study (unresponsive one patient, intolerant three patients, responsive and tolerant but withdrawn at aortic valve prosthesis replacement one patient). Three of the five patients have died: two with documented ventricular tachycardia-ventricular fibrillation. None of the patients has died while on tocainide therapy.

The most frequent cause of the underlying heart disease in this patient group was coronary heart disease with previous myocardial infarction.

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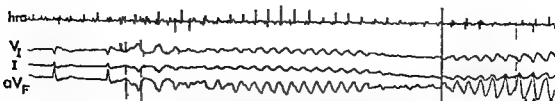


Fig 4 Case 1 Ventricular flutter with shifting axis (*torsade de pointes*) induced by paired ventricular extrastimuli at S-S intervals of 220 to 250 ms while patient was receiving 1,600 mg tocainide/day. Note atrial fibrillation previously induced by rapid atrial pacing. hra = high right atrial electrogram. Other intracardiac recordings have been omitted. V₁, I and aV are standard ECG leads.

Four of the six patients with this condition have withdrawn from the study. Five patients had primary myocardial disease presenting as congestive cardiomyopathy. Two patients had generalized ventricular dilatation and hypokinesia one after surgical replacement of an aortic valve prosthesis and the other after revision of a ventricular-pulmonary artery conduit and residual ventricular septal defect. One patient had normal ventricular function and chronic active myocarditis diagnosed on the basis of findings on serial right ventricular biopsy specimens and cardiac catheterization. One patient had recurrent ventricular tachycardia in the absence of clinically detectable heart disease.

Invasive hemodynamic and angiographic data of recent cardiac catheterizations were available for 13 of the 15 patients. Thirteen patients were in New York Heart Association Functional Class III or IV for dyspnea. Ten patients had cardiomegaly and 11 patients required chronic maintenance digitalis therapy for congestive heart failure. Twelve of the patients had been successfully resuscitated and defibrillated on two or more occasions. Six patients had had previous open heart surgical procedures.

Seven patients had histories of quinidine induced syncope or a paradoxical increase in ventricular ectopic activity while taking quinidine and quinidine-like drugs (Fig 1). In one of these seven patients the administration of quinidine, procainamide and disopyramide consecutively produced spontaneously occurring ventricular tachycardia and ventricular fibrillation. Although ventricular ectopy was frequent in all seven patients ventricular fibrillation had not occurred in the absence of these drugs. Electrocardiograms demonstrated QT prolongation in 11 patients. The QT prolongation was unrelated to identifiable factors in five patients and was secondary to quinidine

like drugs in six patients. Diffuse repolarization abnormalities presenting as prominent U waves were common. The prolonged QT intervals decreased during tocainide therapy (Fig 2). Ventricular fibrillation was most likely to develop when the QT intervals were prolonged because of myocardial injury or drugs (Fig 3).

His bundle electrocardiography combined with programmed ventricular stimulation studies was performed in 10 patients. Sustained ventricular tachycardia could be induced and terminated in seven; however in four patients the tachycardia was rapid hemodynamically unstable and had a shifting electrical axis on the surface electrocardiogram consistent with the atypical ventricular tachycardia *torsade de pointes* (Fig 4) and required emergency cardioversion. A similar type of ventricular tachycardia-ventricular fibrillation occurred in a 9 year old child receiving tocainide alone. The episode of atypical ventricular tachycardia was precipitated by burst exercise and terminated spontaneously several seconds after the child collapsed. The addition of propranolol (20 mg four times a day) to tocainide decreased exercise induced ectopy and prevented further ventricular fibrillation.

Maintenance tocainide therapy ranged from 600 to 3,200 mg daily (1,200 to 3,200 mg daily for adults). The daily maintenance dose was determined by increasing the dosage every 3 to 5 days until the predefined therapeutic goals were achieved or until adverse side effects necessitated a decrease in dosage. Steady state plasma concentrations were not immediately available. On retrospective review effective plasma concentrations ranged from 5 to 19 µg/ml. Blood levels higher than 13 µg and daily tocainide doses higher than 2,400 mg were usually intolerable.

Drug tolerance and side effects. No patient was completely free of side effects during the

Safety evaluation of tocainide in the American Tachycardia Emergency Use Program

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This is a report of the safety evaluation of tocainide in the first 369 patients entered into the American Tachycardia Emergency Use Program. This humanitarian protocol has made tocainide available for emergency use in the treatment of life-threatening intractable ventricular arrhythmias in patients who were unresponsive to or unable to take the approved antiarrhythmic drugs. The most frequent adverse experiences reported were neurologic and gastrointestinal in nature and included dizziness, giddiness, tremors, nausea, vomiting, and anorexia. Adverse experiences resulted in the discontinuation of tocainide in 16% of these patients and were transient and reversible with no conclusive evidence of permanent organ injury. Adverse experiences having special relevance to the safety assessment of new antiarrhythmic agents are discussed, including congestive heart failure, rhythmias, and conduction disturbances, convulsions, lupus erythematosus-like illness, and deaths while in therapy. No significant abnormal trends were observed in routine hematologic and biochemical laboratory screening tests or in ophthalmologic or chest x-ray examinations. An evaluation of the effects of chronic tocainide administration on ECG intervals showed no significant change in P-R or QRS intervals but demonstrated a statistically significant decrease in QT duration. It is concluded that in patients with life-threatening ventricular arrhythmias, tocainide is a safe agent with a favorable risk/benefit ratio.

Tocainide, a new lidocaine-like oral antiarrhythmic agent, has been studied extensively in planned protocols.¹⁻⁴ In addition, this membrane-active agent has been available since 1974 for emergency use in patients with intractable ventricular arrhythmias. Consequently, the American Tocainide Emergency Use Program has provided a unique opportunity to evaluate the safety of tocainide in seriously ill patients treated with the drug for periods up to 41.5 months. The first 369 patients admitted to the program between November 30, 1974, and September 30, 1978, are the subject of this report. These patients entered the protocol in response to requests by their physicians who had reached an impasse in the management of their life-threatening refractory ventricular arrhythmias. Over 200 practicing phy-

sicians participated in the program as investigators during this 4-year period.

The criteria for entering the program were that the ventricular arrhythmias were considered to be life-threatening and the patients were unresponsive to or were unable to take (intolerance or contraindication) the approved antiarrhythmic drugs: quinidine, procainamide, propranolol, and subsequently disopyramide.

Upon entry into the protocol, 60% of these patients were in New York Heart Association Class III or IV, demonstrating respectively moderate or severe compromise of cardiac status. Seventy-one (19%) patients were treated with tocainide for over 1 year, 51 (14%) for 6 to 12 months, and 107 (29%) for 1 to 6 months.

Clinical parameters in safety assessment

Most frequent adverse experiences reported in a long-term open-label open-ended study of patients with severe underlying heart disease

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Table 1 Outcomes of maintenance tocainide treatment in 11 patients with refractory ventricular tachycardia

| Therapy goals | No of patients |
|---------------------------------|----------------|
| Tolerance of effective dosage | 11 |
| Survival while taking tocainide | 15†† |
| Survival and tolerance | 10†† |
| Prevention of | |
| VT with syncope or shock | ■ |
| Symptomatic VT | " |
| Asymptomatic VT | 5 |

Patients tolerated therapy for > 2 mo; four other patients withdrew from trials at 4, 8, 9, and 131 days.

†One patient withdrew from trial at 21 months for surgery; died of left ventricular failure after valve replacement.

††Three patients (all in the group that withdrew) died: two died of ventricular tachycardia, ventricular fibrillation.

entire treatment period in part because of the dosing technique and the patient population. Although pharmacokinetic studies suggest that dosing intervals every 8 to 12 hours should result in maintenance of adequate blood levels for suppression of ventricular ectopy, we found that 6-hour dosing intervals were more effective in suppressing malignant arrhythmias while minimizing dose-related side effects. Four patients required drug administration five to six times per day in order to achieve tolerance. Mild side effects of the central nervous system were experienced by all patients. Ten of the patients complained of mild to severe nausea. Vomiting was infrequent. Gastrointestinal intolerance and a diffuse skin rash developed in three patients during the first week of therapy, and these side effects necessitated the subsequent withdrawal of the three patients from the drug trial on days 7, 8, and 31, respectively. One additional patient developed a mild rash that was managed by temporary dose reduction. In addition to dizziness, tremulousness, and paresthesias, a common side effect of the central nervous system consisted of memory loss and a decreased ability to work with numbers. Although there was a wide variation among individual patients, the presence and severity of most side effects were closely related to the size of each individual dose and the total daily dose. In general, side effects decreased with time and could be reduced by either taking the drug with meals or taking it more frequently.

Drug efficacy Thirteen of the patients had a

favorable response with tocainide alone or in combination. In one patient, the combination of tocainide and propranolol was effective, whereas tocainide alone was associated with increased ventricular ectopy. The one patient who was withdrawn from the study at 4 days because of unresponsiveness had paroxysmal ventricular tachycardia associated with acute coronary insufficiency. The arrhythmia was no longer refractory to lidocaine analogues after saphenous vein bypass surgery. None of the patients died while receiving maintenance tocainide therapy, where as three of the five patients withdrawn from the drug trial because of intolerance died.

Drug efficacy as determined by the predefined therapeutic goals is summarized in Table 1. Two patients had syncope secondary to paroxysmal sustained ventricular tachycardia-ventricular fibrillation. Both patients had omitted one or two medication doses just before the episode. Both patients required hospitalization and were successfully managed. Prolonged ECG monitoring obtained during rehospitalization and through periodic ambulatory ECG monitoring demonstrated a decrease in sustained and nonsustained ventricular tachycardia. Partial or total tocainide withdrawal during follow-up hospitalizations resulted in an increase in ventricular ectopic activity in seven patients. Eight patients have had improvement in their exercise tolerance and have less exertional dyspnea. A clinically significant negative inotropic effect of tocainide has not been observed. Seven patients have had reassessment of left ventricular function by echocardiography, radionuclide imaging, or catheterization techniques during the follow-up period. Comparisons of cardiac index, wall motion, chamber size, and left ventricular end diastolic pressure also suggest that tocainide is well tolerated hemodynamically, even when used for patients with poor left ventricular function.

Discussion

Life-threatening ventricular arrhythmias remain a therapeutic challenge. The currently available antiarrhythmic agents are often ineffective or are not tolerated because of adverse side effects. Occasionally, these agents will increase ventricular ectopy and the vulnerability to ventricular fibrillation. When patients with symptomatic or asymptomatic ventricular tachycardias are being treated, the implied thera-

Table 1 Percentage occurrence of most frequent adverse experiences in 369 patients treated with tocainide

| Adverse experience | % of patients |
|-------------------------------|---------------|
| <i>Gastrointestinal</i> | |
| Nausea | 31 |
| Vomiting | 16 |
| Anorexia | 13 |
| <i>Central nervous system</i> | |
| Dizziness | 31 |
| Lightheadedness | 24 |
| Tremors | 22 |
| Paresthesias | 16 |
| Confusion | 13 |
| Nervousness | 13 |
| <i>Other</i> | |
| Palpitations | 17 |
| Shortness of breath | 13 |
| Rash | 12 |

associated with life threatening refractory ventricular arrhythmias one should anticipate the reporting of a number of adverse experiences because of the long duration of exposure to a variety of factors. This was the case in the Emergency Use Program as most patients reported one or more adverse experiences at some point during the entire period of treatment. Table I shows the percentage occurrence of the most frequent adverse experiences in the 369 patients in this study. The sources of data for this table include not only documented information from the conventional investigator's data form but also all other available information some of which may be considered undocumented. The latter sources include hospital and office charts, physician and nurse's notes, physician's correspondence and reports of the sponsor's site visits and telephone contacts. Patients were included in this table if an adverse experience occurred only once during the entire period of treatment. The majority of reported adverse experiences were neurologic or gastrointestinal in nature. The neurologic experiences appeared to be related to dosing indicating a possible relation to peak blood levels and penetration of the blood brain barrier such as occurs with lidocaine. Although these mostly subjective experiences were sometimes distressful for the patients they were usually transient in nature and reversible with no evidence of permanent organ injury.

Adverse experiences resulting in discontinuation of tocainide. The adverse experiences of greatest importance were those severe enough to result in the discontinuation of tocainide therapy. This occurred in 60 (16%) of the patients in the program. The frequency distribution of these adverse experiences is provided in Table II. Only rarely was a causal relationship between tocainide and the adverse experience tested by a rechallenge with tocainide. In dealing with severely ill patients it is difficult to establish cause and effect relationships for any drug and particularly difficult for an antiarrhythmic agent. Neurologic and gastrointestinal adverse experiences were a primary cause of discontinuation in 48 of the 60 dropouts (80%).

Rash as the only adverse experience accounted for four patient discontinuations. In two patients recurrence of the rash was observed following rechallenge with tocainide. While fever was reported as an adverse experience in only one subject did it subside with discontinuation of tocainide and return with rechallenge. One patient was discontinued because of hepatitis confirmed by a liver biopsy that could not distinguish between infection and a drug reaction. Cytomegalovirus was suggested as a possible etiologic agent by the investigator. Another patient was discontinued because of elevated liver enzymes. This patient had aortic valve replacement just prior to starting tocainide and the possibility of a serum hepatitis must be considered. One patient was discontinued (after receiving 1400 mg of tocainide over 24 hours) because of the development of acute pulmonary edema 5 hours after the last dose. The patient had a previous left ventricular aneurysmectomy and was in New York Heart Association Functional Class IV. Understandably this patient was not rechallenged and other possible inciting factors could not be completely ruled out. One patient was discontinued because of the development of polyarthritis and an elevated antinuclear antibody (ANA) titer. The investigator stated that other explanations could not be dismissed such as the concurrent treatment with disopyramide and the recently discontinued procainamide. One patient was discontinued because of recurrent pericarditis associated with an elevated ANA titer both of which antedated the onset of tocainide therapy. One patient developed what appeared on chest x-ray films to be an interstitial

peutic goal is to prevent spontaneous sustained ventricular tachycardia-ventricular fibrillation and sudden cardiac death. Preventive treatment is based on the assumptions that (1) a reduction in ventricular ectopic activity decreases vulnerability to ventricular tachycardia-ventricular fibrillation and (2) the reduction in ventricular ectopic activity reflects the clinically significant antiarrhythmic properties of the drug in question.

Recent studies have challenged these assumptions. Frequency of premature ventricular contractions and various grades of ventricular ectopy short of bursts of ventricular tachycardia may have limited predictive value in identifying high risk patients.¹² Also, the large day to day variability in ventricular ectopy makes attributing the change in frequency of premature ventricular contractions to a specific antiarrhythmic agent hazardous. The value of programmed ventricular stimulation techniques in identifying high risk subset patients and defining effective long term antiarrhythmic programs remains uncertain. In this setting, clinical observations and descriptive analysis over a long period are essential for documentation of clinically significant antiarrhythmic benefits. The end points of (1) survival, (2) paroxysmal tachycardia with hemodynamic collapse, and (3) symptomatic nonsustained ventricular tachycardia can be clearly defined so that conclusions regarding drug efficacy for an individual patient are possible. In this highly selected patient group, tocainide was therapeutically useful. Conclusions regarding antiarrhythmic drug efficacy in a nonselected population should not be drawn from our experience. However, awareness of several factors common to this group may be useful in identifying patients likely to benefit from tocainide therapy. These factors include responsiveness to intravenously administered lidocaine, quinidine induced syncope or increasing ventricular ectopy with quinidine like medications, primary or secondary Q-T prolongation and shortening of the Q-T interval with maintenance tocainide therapy.

Supporting the importance of prolongation of the Q-T interval, Haynes et al.¹³ reported a high incidence of Q-T prolongation and repolarization abnormalities in patients surviving out of hospital ventricular fibrillation and also noted the continued high risk for repeat episodes of ventricular fibrillation. The association between sudden

death and Q-T prolongation also has been described for postinfarction patients¹⁴ and for patients with hereditary prolongation of the Q-T interval. The frequent occurrence of Q-T prolongation, quinidine induced syncope, and *torsade de pointes* may reflect specific electrophysiologic mechanisms that are advantageously modified by tocainide or lidocaine. These patients may represent a specific subgroup of patients who are likely to benefit from tocainide therapy. Additional investigation is needed to substantiate these relationships.

Simultaneous maintenance digoxin and tocainide therapy was used in 11 of our patients without untoward clinical effects or without alterations in expected blood levels. Combination antiarrhythmic therapy consisting of propranolol and tocainide or quinidine like drugs and tocainide improved antiarrhythmic control achieved by a single drug in higher concentrations. Combination therapy permitted lower dosages and reduced side effects. This apparent complementary interaction probably reflects the different electrophysiologic actions of the drugs and emphasizes the potential importance of an oral lidocaine analogue. Irreversible side effects were not observed in this series. Side effects were common and generally were related to the size of each dose and the total number of milligrams per day. Careful titration between drug efficacy and intolerable side effects can be achieved in most patients.

This experience suggests that tocainide has a place in the treatment of refractory ventricular tachycardia and that chronic maintenance tocainide therapy may be particularly beneficial for patients who are responsive to intravenously administered lidocaine, who present with prolonged Q-T intervals, and who are unresponsive to quinidine like agents.

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pulmonary edema that persisted despite diuretic therapy. A lung biopsy was interpreted as showing *no* interstitial pneumonitis. This patient was afebrile with no rash or joint symptoms and had a normal white cell count and ANA titer. Tocainide was stopped and treatment with corticosteroids begun after which pulmonary function and chest x-ray findings improved. She was not rechallenged with tocainide and other possible causes were not ruled out.

Special adverse experiences in antiarrhythmic therapy. In the safety evaluation of a new antiarrhythmic agent there are several adverse experiences of particular importance. These include increased congestive heart failure in increased ventricular arrhythmia, aggravation of preexisting cardiac conduction disturbances, convulsions and a lupus erythematosus-like syndrome. In the Emergency Program no causal relationship with tocainide to these experiences could be definitely established. Even if a causal relationship were established between tocainide and such effects, the comparison with conventional antiarrhythmic agents would be most favorable.

Table III exhibits these special adverse effects for the 369 Tocainide Emergency Program patients. There were five patients in whom the initiation of tocainide therapy was reported to have possibly aggravated severe preexisting heart failure. All five patients were in New York Heart Association Functional Class IV before tocainide treatment. Three had a diagnosis of cardiomyopathy and two had coronary disease with old myocardial infarction. Only one of the patients was discontinued because of this experience and four of the patients were known to subsequently die of heart failure. It is of interest that a number of patients who were unable to tolerate disopyramide or propranolol because of heart failure were subsequently able to tolerate tocainide.

Only four patients who received an adequate trial of tocainide therapy were stopped because of an alleged increase in ventricular arrhythmia occurring during initiation of therapy. Of interest, at least eight long-term tocainide responders with abolition or substantial reduction of life-threatening arrhythmic events while on tocainide had been uncontrolled and had manifested a prolonged QT interval during prior treatment with quinidine, procainamide and disopyramide.

There were two patients with preexisting car-

Table II Adverse experiences resulting in discontinuation among 369 patients

| Adverse experience | No. of patient |
|---|----------------|
| Neurologic | 74 (6.5%) |
| Gastrointestinal | 1 (3.2%) |
| Neurologic/gastrointestinal | 11 (3.0%) |
| Neurologic/sun sensitivity | 1 (0.7%) |
| Neurologic/supraventricular tachycardia | 1 (0.2%) |
| Rash/fever/neurologic | 1 (0.2%) |
| Rash | 4 (1.1%) |
| Rash/fever/hepatitis | 1 (0.2%) |
| Elevated liver enzymes | 1 (0.2%) |
| Increased congestive heart failure | 1 (0.2%) |
| Arthritis | 1 (0.9%) |
| Recurrent pericarditis | 1 (0.9%) |
| Interstitial pneumonitis | 1 (0.9%) |
| Total | 60 (16.3%) |

Table III Adverse experiences of particular relevance in antiarrhythmic drug therapy

| Adverse experiences | No. of possible occurrences in 369 patients |
|---|---|
| Increased congestive heart failure during initiation of tocainide therapy | 5 (1.4%) |
| Increase of ventricular arrhythmia during initiation of tocainide | 4 (1.1%) |
| Possible aggravation of preexisting cardiac conduction disturbances | 2 (0.5%) |
| Convulsions | 2 (0.5%) |
| Lupus erythematosus-like illness | 3 (0.8%) |

diac conduction disturbances that may possibly have been aggravated by tocainide although other explanations exist for the observed conduction changes. One patient who exhibited transient second degree A-V block was concurrently receiving digoxin and a beta blocker and was continued on tocainide for 36 months without any subsequent conduction problem. The other patient had advanced degrees of A-V block but had recently undergone mitral valve replacement which may be associated with transient or permanent changes in A-V conduction.

Convulsions were reported to occur in two patients while on tocainide; no other obvious explanation for these convulsions exists. Both patients were women over 80 years of age, one

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had previous brain damage from multiple cardio pulmonary resuscitations and the other had a tocainide blood level of 20 µg/ml

There were three patients in whom a lupus erythematosus-like illness was reported while on tocainide. Two of these were discontinued and had confounding factors preventing the determination of a causal relationship to tocainide. The third patient had a prior history of a procainamide induced lupus like illness. A myocardial biopsy done before tocainide was started revealed myocarditis and the possibility of a preexisting collagen disease was raised. While on tocainide he had intermittent arthralgias, rash, fever, light sensitivity, and proteinuria. The ANA titer fluctuated between negative and positive for 38 months of continuous tocainide treatment during which the drug was never stopped.

Deaths during tocainide therapy. Thirty three patients died while on tocainide therapy. Of these patients 28 had a diagnosis of coronary artery disease and five had cardiomyopathy. Prior to tocainide therapy 58% of the 33 patients were in New York Heart Association Functional Class IV and 85% were in Class III or IV which placed them in a high risk category for death. Thirteen of the deaths (39%) were characterized as arrhythmic or sudden. Seven patients died of acute myocardial infarction, eight patients of progressive heart failure, one of a cerebrovascular accident, one of a pulmonary embolus, one of pneumonia, and in two patients the causes were unclear. Eleven of the thirteen arrhythmic deaths occurred in patients with a documented history of resuscitation for ventricular fibrillation prior to tocainide therapy. In no case did either the patient's physician or the sponsor find conclusive or even strongly suggestive evidence that tocainide caused the death.

Laboratory parameters in safety assessment

No significant abnormal trends were detected in the laboratory safety screening data. This assessment included periodic measurements of hemoglobin, hematocrit, red blood cell counts, reticulocyte counts, white blood cell and differential counts, platelet counts, blood urea nitrogen, creatinine, liver function, electrolytes, Coombs tests, ANA titers, urinalyses, and chest x-ray films. Routine ophthalmologic examinations detected no specific toxic effect on the eye.

Electrocardiography as a parameter of drug safety was the subject of special study. The Tocainide Emergency Use Program afforded a unique opportunity to evaluate the effects of long term oral antiarrhythmic therapy on ECG intervals in contrast to protocols in which tocainide was administered orally for only brief periods^{1,2} or intravenously.^{3,4} Accordingly, an evaluation of P-R interval, QRS duration, and rate corrected Q-T interval was performed retrospectively on a group of 43 emergency patients who had received the drug for at least 6 months with a mean of 16 months. Chronic tocainide therapy produced no significant change in P-R interval or QRS duration but resulted in a statistically significant decrease in Q-T duration. This latter observation may have been due to a tocainide effect or alternatively to the discontinuation of quinidine like drugs just before or during tocainide therapy.

Conclusions

Based on this analysis of the first 369 patients in the Tocainide Emergency Program our conclusions are as follow: (1) Adverse experiences with tocainide were primarily neurologic and gastrointestinal in nature. (2) Adverse experiences were transient and reversible with no conclusive evidence of permanent organ injury. (3) Adverse experiences resulted in discontinuation of tocainide in 16% of patients. (4) In patients with life threatening ventricular arrhythmias, tocainide is a safe agent with a favorable risk/benefit ratio.

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Repetitive responses to ventricular extrastimuli: incidence, mechanism, and significance

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Repetitive ventricular responses are commonly induced by programmed ventricular stimulation. The mechanisms and clinical significance of these repetitive responses specifically their relationship to malignant ventricular tachyarrhythmias have not been clarified. The present study was designed to (1) determine the incidence of such responses, (2) analyze the different types of repetitive ventricular responses, and (3) assess their relationship to clinical arrhythmias.

Methods and materials

The study population included 400 consecutive patients undergoing electrophysiologic evaluation in whom ventricular stimulation was per-

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formed between July 1973 and January 1978 at the Hospital of the University of Pennsylvania. Programmed ventricular stimulation was done routinely in all patients undergoing electrophysiologic evaluation of conduction and rhythm disorders. This group included 289 patients with organic heart disease and 111 patients with no clinical evidence of heart disease. Ischemic heart disease (diagnosed by previous myocardial infarction, typical angina pectoris, or positive coronary angiography) was the most common underlying organic disease (197 patients). Thirty patients had valvular heart disease, 20 had cardiomyopathy, 18 had congenital heart disease, and the remainder (24) had hypertensive cardiovascular disease. No patients in this group were within two weeks of myocardial infarction. Fifty-eight patients were studied because of documented sustained ventricular tachycardia or ventricular fibrillation. All studies were performed in the nonsedated postabsorptive state after informed consent was obtained. Antiarrhythmic agents were not administered in the 24 hours prior to study.

Three to five electrode catheters were inserted percutaneously through the femoral and/or antecubital veins and were positioned under fluoroscopic control in the right atrium, coronary sinus, atrioventricular junction, His bundle, recording and in the right ventricular apex. In 48 patients undergoing evaluation of ventricular tachycardia or ventricular fibrillation, an addi-

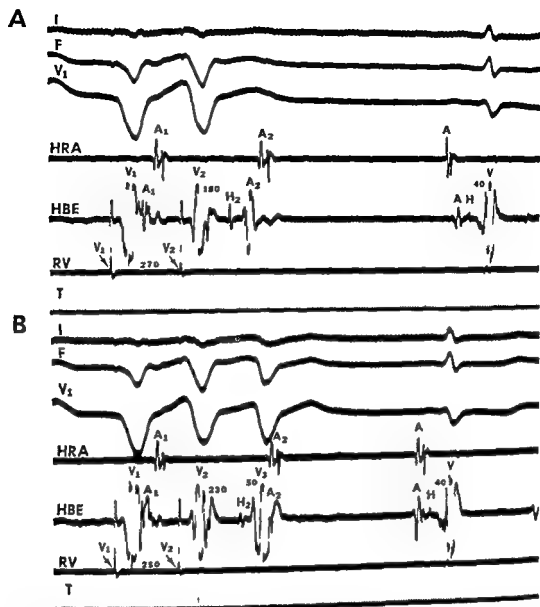


Fig 1 Initiation of bundle branch reentry. Surface Leads I, aV_r (F) and V are shown with intracardiac electrograms from the high right atrium (HRA), His bundle recording site (HBE) and right ventricle (RV). In panel A after the eighth complex (V_j) at paced ventricular cycle length of 600 msec, a premature ventricular stimulus (V_j) is introduced at a coupling interval of 270 msec. Retrograde His Purkinje delay (V_j H) of 180 msec results. In panel B at a shorter coupling interval (V_j V = 250 msec) a critical degree of V_j H delay occurs and results in an extra ventricular complex due to bundle branch reentry. Note the H V is 50 msec, which is slightly longer than the H V during sinus rhythm (40 msec). Note the similarity in morphology between the premature complex and the bundle branch reentrant complex (V_j). A, H, V are atrial, His bundle and ventricular electrograms, respectively. T = time lines.

tional electrode catheter was inserted into either the femoral artery percutaneously or into the brachial artery by cutdown and was advanced to the left ventricle for left ventricular recording and/or stimulation. Two or three surface electrocardiographic leads and intracardiac electrograms from different sites were displayed on a multichannel oscilloscope (Electronics for Medi-

cine DR 16 White Plains, N.Y.) and were simultaneously recorded on magnetic tape (Honeywell 5600C). Data were subsequently retrieved on photographic paper for analysis at paper speeds of 100 to 200 mm/sec.

Ventricular stimulation was performed using a programmable constant current impulse generator (Bloom Associates Ltd, Narberth, Pa).

Treatment of ventricular arrhythmias with oral tocainide

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This is a report of a multicenter open study of the use of tocainide, a new lidocaine-like antiarrhythmic with a high oral bioavailability, in the treatment of life-threatening ventricular arrhythmias refractory to other therapy. The majority of patients have received 1,200 to 2,400 mg daily in divided doses and have been treated for over 6 months and some for longer than 3 years. Overall, 61% of the patients responded successfully to tocainide therapy. In the 252 patients with documented severe symptomatic arrhythmias, 71% responded, and the majority (87.4%) showed a total abolition of symptomatic events. Gastrointestinal and central nervous system events were the most common adverse experiences, and 10% had to discontinue therapy; however, the remaining 89% tolerated tocainide satisfactorily.

Lidocaine is the antiarrhythmic agent of choice for the acute intravenous treatment of ventricular arrhythmias, especially those occurring early after acute infarction. However, lidocaine is extensively metabolized by the liver in a first-pass effect and therefore cannot be given orally. Consequently, it has been necessary to use other antiarrhythmics for continuous oral therapy. Recent efforts directed toward the development of oral antiarrhythmics of the same type as lidocaine resulted in the synthesis of tocainide, a lidocaine analogue that has a high bioavailability when given orally and has an excellent spectrum of antiarrhythmic activity. In this study, we report on the use of tocainide for the chronic treatment of ventricular arrhythmias in a multicenter study involving many investigators. The arrhythmias were refractory to other therapy, and all patients had either failed to respond to or were unable to tolerate other antiarrhythmic agents including quinidine, procainamide, disopyramide, and propranolol.

Materials and methods

A total of 819 patients with severe refractory ventricular arrhythmias received the drug, of whom 628 had

an adequate trial of treatment and were documented sufficiently to allow an evaluation of the efficacy of tocainide therapy.

Males outnumbered females by more than 2:1, and their ages ranged from 9 to 86 years, with the majority of patients being between 40 and 70 years old (Table I).

The most common etiology of the patients' cardiac disease was atherosclerotic heart disease; however, a significant number of patients had cardiomyopathies or valvular heart disease (Table II).

The patients had either ventricular tachycardia or frequent and/or complex ventricular ectopic beats. The severity of their cardiac status was evaluated, and 63% of them were categorized as New York Heart Association Class III or IV prior to tocainide therapy (Table III).

A further indication of the severity of the patients' disease was the fact that 54% of them were receiving digitalis glycosides and 42% required treatment with diuretics at some time during the study.

Tocainide therapy was initiated on a 1,200 mg daily dose either as 400 mg tid or 600 mg bid, which was then adjusted according to the patient's response. The majority of patients received 1,200 to 2,400 mg daily in divided doses as shown in Table IV, which shows the final regimen the patient received regardless of whether

Astra Pharmaceutical Products, Inc., Framingham, Mass.
Contracted by Michael D. Young, M.D., Astra Pharmaceutical Products, Inc., P.O. Box 1089, Framingham, MA 01701.

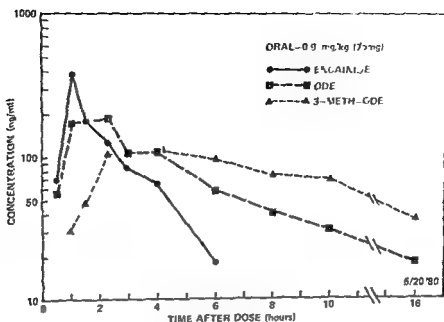


Fig 7 Log of plasma concentration (C_p) of encainide and two of its major metabolites after oral administration in a patient with asymptomatic PVCs (Courtesy Dr Robert Mavol Mead Johnson Pharmaceutical)

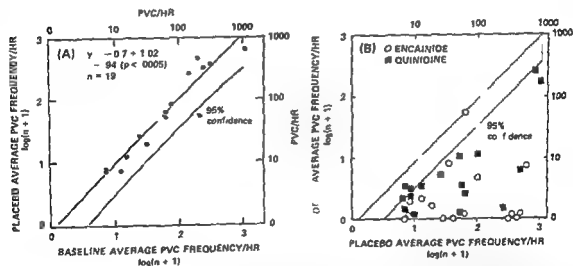


Fig 8 Response of the $\log(n+1)$ of PVCs in patients treated with encainide and quinidine on a plot of two prior determinations made by a linear regression analysis and the establishment of 95% confidence intervals (From Sami M Harrison DC Kraemer II Houton N Shumaker B DeBusk RF The antiarrhythmic efficacy of encainide and quinidine Validation of a new model for drug assessment Am J Cardiol (In press))

Comparison of encainide with quinidine The antiarrhythmic efficacy of encainide and quinidine was compared in 20 ambulatory men with a mean age of 56 years. These patients had a history of chronic ischemic heart disease and were studied in a longitudinal crossover design with PVCs recorded on treadmill exercise tests and 24 hour ambulatory ECGs. All patients had a

baseline evaluation before entering the study and were then randomized to one of two drug sequences consisting of 2 weeks of placebo followed by 2 weeks of treatment with the first drug and a 1 week washout period after which the sequence was repeated with the second drug.

In this comparison the reduction of average frequency of PVCs per hour on ambulatory ECGs

Table I Patients demographic data

| Age (yr) | No | Male (%) | Female (%) |
|----------|-----|----------|------------|
| 0-39 | 83 | 47 | 53 |
| 40-69 | 438 | 76 | 24 |
| 70-89 | 96 | 72 | 28 |
| Unknown | 11 | 45 | 55 |
| Total | 628 | 71 | 29 |

Table II Etiology of patients arrhythmias

| Etiology | % of patients |
|-------------------------------|---------------|
| Atherosclerotic heart disease | |
| Post AMI | 61 |
| Other | 10 |
| Cardiomyopathy | 10 |
| Mitral valve prolapse | 5 |
| Rheumatic heart disease | 4 |
| Unknown | 10 |

AMI = acute myocardial infarction.

Table III New York Heart Association functional classification of cardiac status prior to treatment

| Class | No |
|---------|-----|
| I | 53 |
| II | 139 |
| III | 209 |
| IV | 122 |
| Unknown | 106 |

er a lower dose had been adequate for some time previously

The treatment is still ongoing. At the time of this review of the program, the majority of the patients had been treated for over 6 months and some for more than 3 years (Table V).

Results

Efficacy was assessed by the individual physician responsible for the patient. The parameters used were clinical response and laboratory testing including Holter monitoring, telemetry, rhythm strips, exercise testing, controlled weaning after successful therapy, and in a few cases programmed electrical stimulation studies.

In addition, we have arbitrarily decided that no patients would be considered to have been successfully treated if therapy was not given continuously for at least 1 month. Therefore, this is an

Table IV Final treatment regimen

| Total daily dose (mg) | Daily regimen (mg) | No of patients | % of patients (n = 628) |
|-----------------------|--------------------|----------------|-------------------------|
| 1,200 | 400 q8h | 109 | 17 |
| 1,200 | 600 q12h | 30 | 5 |
| 1,600 | 400 q6h | 37 | 6 |
| 1,800 | 600 q6h | 147 | 23 |
| 2,400 | 600 q6h | 30 | 5 |
| 2,400 | 800 q6h | 73 | 12 |

evaluation of the efficacy of chronic oral therapy with tocainide.

Overall, 61% of the patients responded successfully to tocainide (Table VI). Of the 628 patients, 252 (40%) had documented severe symptomatic arrhythmias and their symptomatic response to treatment was dramatic. A total of 178 patients (71%) with symptomatic ventricular arrhythmias responded to tocainide, and the majority of such responders (87%) showed total abolition of symptomatic arrhythmic events as shown in Table VII.

Also, a detailed evaluation of the symptomatic patients showed there was a greater than 90% reduction in emergency hospital admissions, DC cardioversions, syncope, or presyncope during treatment with tocainide (Table VIII).

Tocainide had no clinically significant negative inotropic effect and was not noted to prolong QT or QRS intervals during this chronic therapy study. We obtained ECG data from patients on chronic therapy in excess of 6 months (Table IX). The early during treatment values were obtained from the first tracing taken after a steady state level of tocainide had been reached, and the late during treatment values were obtained from the last tracing available for each patient, but in no case were these values obtained less than 6 months into therapy. The statistically significant reduction in QT interval was not considered to be clinically significant.

Side effects were generally either gastrointestinal or neurologic, and of the 628 patients, only 11 (1.3%) had to discontinue therapy because of an adverse experience as shown in Table X.

Discussion

Over a period of almost two decades, lidocaine has become established as the most effective agent for the suppression of ventricular arrhythmias.

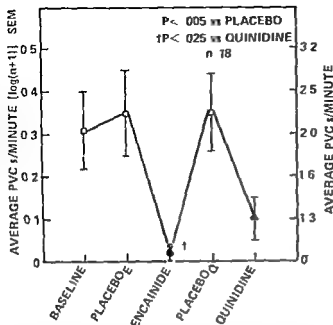


Fig 9 Mean and SEM for average frequency of PVCs in 20 patients determined by ambulatory monitoring while patients were receiving no drug (baseline) placebo before encainide and placebo, before quinidine. Average log (n + 1) and average PVCs per minute are shown. (From Sami M Harrison DC, Kraemer H, Houston N, Shinesaks B, DeBusk RF. The antiarrhythmic efficacy of encainide and quinidine. Validation of a new model for drug assessment. *Am J Cardiol* (In press).)

was greater with encainide than with quinidine ($P > 0.01$). Similarly, reductions in average frequencies of PVCs per minutes on treadmill testing were greater with encainide than with quinidine ($P > 0.02$). Encainide suppressed all PVCs in 44% of the patients and reduced them by at least 80% in 88% of the patients. Encainide suppressed complex PVCs in 100% of the patients during 24 hours of ambulatory ECG recording. In contrast, none of the patients demonstrated total PVC depression with quinidine and only 44% demonstrated at least 80% reduction in PVC frequency with only 53% of the patients showing suppression of all complex PVCs during the 24-hour period of ambulatory ECG recording.

The responses to quinidine and encainide were compared by means of a new statistical technique for antiarrhythmic drug efficacy based upon a linear regression analysis with determination of 95% and 99% confidence intervals when the variability for baseline and placebo measurements was compared. Analysis was performed on a log (PVC frequency + 1) (Fig. 8). When absolute responses to quinidine and encainide were com-

pared with placebo, the results showed a distinct advantage for encainide (Fig. 9).

A systematic evaluation of side effects of the drug was performed in this study. Comparison of side effects on placebo and during encainide and quinidine therapy are illustrated in Table III. On placebo, mild lightheadedness or dizziness and mild gastrointestinal effects were frequently noted. With encainide therapy, lightheadedness and dizziness of mild to moderate severity were noted in 11 of the patients. This did not require discontinuation of the drug in any patients, although the drug dose was lowered in four patients. With quinidine, gastrointestinal side effects were common, occurring in 11 of 20 patients requiring reduction of the drug in three. Fever was present in five patients treated with quinidine and a rash occurred in three while they were receiving quinidine (Table III).

Antiarrhythmic efficacy of encainide in patients with refractory recurrent arrhythmias. New antiarrhythmic drugs are frequently studied in patients with refractory arrhythmias or in patients who cannot tolerate antiarrhythmic drugs currently available. We have used encainide in 38 patients with recurrent ventricular tachycardia meeting these entry criteria. In this group of patients, the usual dose of encainide required ranged from 150 to 250 mg/24 hr. Encainide completely eliminated recurrent ventricular tachycardia in 54% of the patients through 6 months of therapy and 29% of the patients between 18 and 30 months of therapy. Twelve patients (32%) had side effects possibly due to encainide. In four patients, a ventricular arrhythmia of longer duration or more resistant to other forms of therapy occurred while the patient was receiving encainide. In these patients, it is reasonable to conclude that encainide may have worsened the arrhythmia.

In our studies, QRS prolongation appeared to correlate with antiarrhythmic effects in these patients with difficult and recurrent arrhythmias. However, these studies suggest that encainide is a safe and well tolerated antiarrhythmic drug in preventing recurrent ventricular tachycardia.

Discussion

Preliminary studies with encainide suggest that this agent has important antiarrhythmic effects that permit its classification into a subcategory of Class I agents now available. Our studies to date

Table V Duration of treatment with tocainide

| Duration of treatment | No of patients |
|-----------------------|----------------|
| Greater than 3 yr | 16 (3%) |
| From 2 to 3 yr | 46 (7%) |
| From 1 to 2 yr | 88 (14%) |
| 6 mo to 1 yr | 110 (18%) |
| From 1 to 6 mo | 156 (25%) |
| Less than 1 mo | 212 (34%) |

miat.¹⁶ Unfortunately lidocaine cannot be used effectively by oral administration. Tocainide is a lidocaine like agent that is active orally. It has been reported to be effective in the treatment of ventricular arrhythmias in patients with coronary valvular and myopathic disease.⁷

This study evaluated the responses to tocainide therapy of patients with severe refractory ventricular arrhythmias and the program was initiated as a humanitarian effort to treat these particularly difficult cases. The severity of the patients' condition was documented by the fact that 63% were New York Heart Association Class III or IV when tocainide therapy commenced and also by the fact that all the patients had failed to respond adequately to or could not take full dosages of other oral antiarrhythmic agents including quinidine, procainamide, propranolol, and when available, disopyramide. In fact many patients could not be controlled adequately even on combinations of these agents.

The etiologies of the patients' cardiovascular diseases are shown in Table II and clearly indicate that although the majority of patients had atherosclerotic heart disease, a considerable number had valvular and myopathic disease.

Much has been written about the difficulty inherent in evaluating the response to antiarrhythmic therapy because of the variability in the frequency of ventricular ectopic beats in long term ECG monitoring.¹⁷ Despite this, long term ECG monitoring is the basic parameter used to monitor the response to an antiarrhythmic agent. Over 570 physicians were involved in this multicenter study of 628 patients and they evaluated the response to tocainide therapy by means of telemetry, ECG rhythm strips, 24 hour Holter recordings, exercise testing, and in a few cases programmed electrical stimulation. Also noted was the presence or absence of symptoms of ventricular arrhythmias. In addition, since these patients required maintenance therapy for con-

Table VI Response to treatment with tocainide

| Therapeutic response | No of patients |
|----------------------|----------------|
| Success | 383 (61%) |
| Failure | 245 (39%) |

Table VII Degree of response of severe symptomatic arrhythmias to tocainide therapy

| Duration of treatment | Total abolition | Substantial reduction | No response |
|-----------------------|-----------------|-----------------------|-------------|
| Over 3 yr | 12 | — | — |
| 2 to 3 yr | 22 | 3 | — |
| 1 to 2 yr | 23 | 10 | — |
| 6 mo to 1 yr | 36 | 11 | ? |
| 1 to 6 mo | 61 | 5 | 19 |
| Less than 1 mo | — | — | 54 |
| Total | 154 (61%) | 24 (10%) | 74 (39%) |

siderable periods, this study evaluated treatment in excess of 1 month's duration. That is to say, although patients might be judged to have failed to respond to tocainide after an initial trial of as little as 3 days, no patients were evaluated as showing a successful response to tocainide unless they had had at least 1 month's therapy. In fact the majority of patients had been treated for over 6 months with tocainide.

Overall, 61% of the patients responded successfully to tocainide (Table VI) despite the refractory nature of the arrhythmias being treated and the most usual dosage was 600 mg t.i.d.

Of the 628 patients, it was particularly interesting to consider the symptomatic response to treatment of the 252 who had documented severely symptomatic arrhythmias. Severe symptoms were defined as repeated occurrence of hospitalization, ventricular tachycardia, ventricular fibrillation, DC cardioversion, syncope, or multiple presyncopal episodes. A total of 178 patients (71%) with these severe symptomatic ventricular arrhythmias responded to tocainide and of them the majority (87%) showed a total abolition of all symptomatic arrhythmic events (Table VII). Also a detailed evaluation of the symptomatic patients showed there was a greater than 90% reduction in emergency hospital admissions, DC cardioversions, syncope, or presyncope during treatment with tocainide (Table VIII). This represents a considerable improvement in

Table III Side effects of encainide, quinidine and placebo

| Side effects | Placebo (n = 20) | | Encainide (n = 10) | | Quinidine (n = 14) | |
|---|---------------------|---------------------|-----------------------|---------------------|-----------------------|---------------------|
| | Mild | Moderate/ severe | Mild | Moderate/ severe | Mild | Moderate/ severe |
| Lightheadedness or dizziness | 4 | 2 | 2 | 4 | 5 | 1 |
| Gastrointestinal (nausea, vomiting, diarrhea) | 8 | 1 | 2 | 0 | 6 | 0 |
| Fever | 3 | 1 | 0 | 0 | 2 | 3 |
| Rash | 1 | 1 | 2 | 0 | 2 | 1 |

n = Number of patients

Dose lowered to .5 mg in four patients

Dose lowered to .00 mg in three patients.

suggest that this agent has important antiarrhythmic effects when administered to patients with frequent and complex ventricular arrhythmias.^{4,11}

Electrophysiologic studies in animals and humans demonstrate prolongation of His Purkinje conduction as evidenced by widening of the QRS complex and prolongation of the H-V intervals.⁷ Little or no effects were noted on the sinus node, atrial refractoriness, A-V node refractoriness or ventricular refractoriness. Elevations of ventricular fibrillation threshold in animal studies suggest that this agent may be useful in preventing sudden death.

In patients with normal ventricular function or only mildly altered ventricular function, encainide produces little or no hemodynamic effects. In patients with markedly depressed ventricular function, elevated left ventricular end diastolic pressures and lowered cardiac output, encainide reduces cardiac output slightly without altering the contractility indices or left ventricular end diastolic pressure. These small changes in hemodynamics are in marked contrast to those recently reported for disopyramide.

Antiarrhythmic efficacy In patients with ventricular premature beats, both the oral and intravenous administration of encainide proved to be highly effective in reducing the frequency and complexity of ventricular premature beats. In those patients with recurrent and resistant ventricular tachycardia, encainide proved effective in more than half of such patients even when all other antiarrhythmic drugs had failed. The maintenance of these patients for 18 to 30 months on encainide without recurrence of ventricular tachycardia seems important.

In comparative studies with quinidine, encainide was shown to be more effective in reducing ventricular premature beats and complex ventricular arrhythmias on ambulatory arrhythmia monitoring and treadmill testing. Side effects for the drugs were of equal frequency in this crossover study design. The side effects of encainide were those of central nervous system origin and those of quinidine of gastrointestinal origin or fever or rash. A greater reduction in ventricular premature beats and complex forms was noted with encainide than with quinidine.

Conclusions

Encainide is an important new antiarrhythmic drug. It has proved to be highly effective in reducing ventricular premature beats and recurrent ventricular tachycardia. There are few hemodynamic side effects. The agent produces marked increase in His-Purkinje conduction and a widening of the QRS complex, which appears to occur on a dose-related and plasma concentration basis. Side effects of the drug are not severe, although in a few patients the drug appears to enhance the occurrence and severity of reentry cardiac arrhythmias.

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Table VIII Symptomatic events in 252 severely symptomatic patients

| Arrhythmic events | No of patients | No of occurrences | | % Reduction |
|-------------------------------|----------------|-------------------|------------------|-------------|
| | | Before treatment | During treatment | |
| Emergency admission for VT/VF | 129 | 364 | 26 | 93 |
| DC cardioversion for VT/VF | 112 | 512 | 17 | 97 |
| Episodes of syncope | 104 | 403 | 11 | 97 |
| Episodes of presyncope | 57 | 7.6 | 6 | 99 |

Table IX ECG intervals before and during long term tocainide therapy in 22 patients

| Evaluation period | P R interval (mean \pm SD) | QRS interval (mean \pm SD) | QT interval (mean \pm SD) |
|------------------------|------------------------------|------------------------------|-----------------------------|
| Pretreatment | 173 \pm 0.021 | 0.093 \pm 0.030 | 0.410 \pm 0.044 |
| Early during treatment | 0.171 \pm 0.021 | 0.093 \pm 0.030 | 0.431 \pm 0.046 |
| Late during treatment | 0.175 \pm 0.020 | 0.095 \pm 0.029 | 0.436 \pm 0.055 |

0.05 > P > 0.01

Table X Adverse experiences resulting in discontinuation of tocainide in 628 patients who were valid for evaluation of efficacy

| Reason for discontinuation | % of patients |
|----------------------------|---------------|
| CNS | 4.9 |
| CI | 2.4 |
| CNS/GI | 1.6 |
| Rash | 2.1 |
| Increased CHF | 0.3 |
| Total | 11.3 |

Abbreviations: CNS = central nervous system; GI = gastrointestinal; CHF = congestive heart failure

the morbidity rate for these severely symptomatic patients

Tocainide had no clinically significant negative inotropic effect in hemodynamic studies and was not noted to prolong Q T or QRS intervals in electrophysiologic studies. During this chronic therapy study we obtained ECG data from patients on therapy in excess of 6 months. The early during treatment values (Table IX) were obtained from the first tracing taken after a steady state level of tocainide had been reached and the late during treatment values were obtained from the last tracing available for each patient but in no case was the value obtained less

than 6 months into therapy. There was no significant prolongation of either Q T or QRS intervals. A statistically significant reduction in Q T interval was seen however this was not considered to be clinically significant.

The side effects to tocainide are generally those to be expected for a lidocaine analogue and have been discussed in detail elsewhere.¹ In this study only 11% of the 628 patients treated with tocainide had to discontinue therapy because of side effects and the remaining 89% tolerated the tocainide therapy satisfactorily.

We conclude that tocainide is an effective and safe agent for the management of refractory ventricular arrhythmias.

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Studies with aprindine

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Aprindine is a very effective antiarrhythmic agent with a narrow therapeutic toxic ratio. It has been used successfully in treating patients who have both supraventricular and ventricular tachyarrhythmias. Aprindine slows conduction in all cardiac fibers and suppresses digitalis induced after-depolarizations. Voltage-clamp studies indicate that aprindine in higher doses suppresses the slow inward current in frog atria. In the dog subjected to coronary artery occlusion aprindine may be arrhythmogenic or have no effect on the development of arrhythmias depending on the temporal relationship between time of administration and time of occlusion.

Aprindine an antiarrhythmic agent with prominent local anesthetic effects was developed and used initially in Belgium. It is available clinically throughout most of Europe and is being evaluated as an investigational agent at a number of centers in the United States.

Clinical experience

Early studies¹ established aprindine as an effective antiarrhythmic agent against a variety of supraventricular and ventricular arrhythmias that occurred in patients with different types of heart disease.

In our initial experience with aprindine we treated 23 patients with recurrent ventricular tachycardia (10 patients) or recurrent ventricular tachycardia and ventricular fibrillation. In the group with only ventricular tachycardia aprindine prevented further episodes in eight patients; failed to prevent ventricular tachycardia in one patient and converted sustained episodes of ventricular tachycardia to short asymptomatic

bursts in one patient. In the group with ventricular tachycardia and ventricular fibrillation aprindine prevented further recurrences in all but one patient who continued to have recurrent episodes of ventricular tachycardia. One responder had to stop taking the drug because of intolerable side effects. Thus among the 23 patients aprindine was not tolerated by one patient and failed to control the ventricular arrhythmia in two patients. In five responders aprindine plus propranolol (one patient) aprindine plus quinidine (three patients) and aprindine plus permanent ventricular pacing (one patient) achieved better suppression than aprindine alone. Subsequent to this first study we successfully treated seven patients who had ventricular tachycardia associated with mitral valve prolapse.¹

Aprindine has also been used to treat patients with supraventricular arrhythmias.¹ Recently we reported our experience with the use of aprindine in treating 10 patients with recurrent or continuous supraventricular tachycardia that was difficult to control with conventional arrhythmic agents. Nine patients had Wolff Parkinson White syndrome. During administration of aprindine circus movement supraventricular tachycardia could no longer be initiated in four patients and was initiated with difficulty in two patients and with greater ease in two patients. In one patient aprindine therapy slowed the ventricular response during atrial

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IV Antiarrhythmic studies with newer agents

Encainide A new and potent antiarrhythmic agent

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Encainide is a potent Class I antiarrhythmic drug that prolongs conduction in the His Purkinje system. It produces only minimal hemodynamic changes in the normal or depressed left ventricle. Studies to date demonstrate excellent effectiveness against ventricular arrhythmias and in comparative studies with quinidine, encainide was superior in reducing the frequency and complexity of ventricular premature beats in patients late after myocardial infarction.

Although a number of new antiarrhythmic agents have been introduced for clinical trials in the United States during the past decade, there continues to be a need to find more potent and safer new antiarrhythmic agents.¹ No available agent has proved to be entirely satisfactory in preventing sudden arrhythmic deaths in coronary artery disease and cardiomyopathies. On the other hand, several new agents have been documented to be effective in reducing the frequency of less serious ventricular arrhythmias in patients in whom they are tried.

Another shortcoming of available antiarrhythmic agents is their limiting pharmacokinetic properties. They are not ideal in that they must be administered on a schedule of frequent dosing and several of them are metabolized or excreted rapidly, thereby lacking a prolonged duration of action.

Encainide, which has a new molecular structure, was recently introduced for clinical trial as an antiarrhythmic agent. Its cellular effect is to decrease phase zero of the action potential (dV/dt), thereby placing it among Class I antiarrhythmic drugs. It produces little change in the duration of the action potential when studied in isolated cells, suggesting that it would have little effect on repolarization in the intact heart.

Methods and results

During the past 3 years we have performed extensive studies with encainide to elucidate its electrophysiologic effects, its pharmacokinetics, its antiarrhythmic spectrum of activity, and its safety when administered to patients with heart disease. The scope of our studies is outlined in Table I.

Electrophysiologic studies in animals. After cellular studies demonstrated that encainide has the potential for being an antiarrhythmic drug with high potency, it was evaluated in a series of animal studies to detect its effect on cardiac conduction. Mongrel dogs anesthetized with chloralose were divided into four groups. Group 1 was a control group. Groups 2, 3, and 4 were groups to be administered encainide in a dose of 0.3, 0.9, and 2.7 mg/kg body weight, respectively, during an intravenous infusion of 15 minutes duration. Plasma concentrations of drug, blood pressure, electrocardiograms, and atrial and His bundle electrograms were recorded before, during, and after administration of the drug for a total of 120 minutes. Heart rate, A-H, and H-V intervals, the QRS complex, and QT intervals were measured every 5 minutes during sinus rhythm and with a constant heart rate provided by atrial pacing. In addition, sinus node recovery times, atrial and atrioventricular (A-V) nodal and left ventricular refractory periods were measured before and immediately after infusion and every 30 minutes for 2 hours.

The plasma concentrations of the drug that were achieved in these animals are illustrated in

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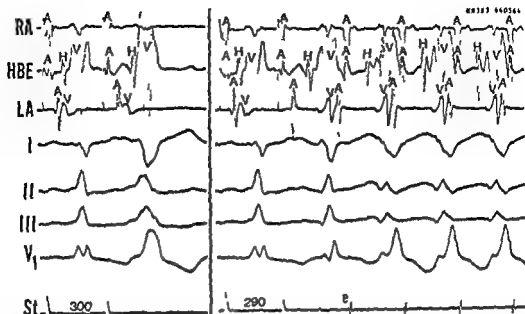


Fig 1A Control recording before treatment with aprindine. Determination of antegrade effective refractory period of accessory pathway and initiation of paroxysmal supraventricular tachycardia in a patient with type A Wolff Parkinson White syndrome. After the last driven impulse of the basic train, premature stimulation of right atrium at a coupling interval of 300 msec resulted in antegrade conduction over the accessory pathway. Activation of bundle of His occurred after onset of QRS complex. Premature right atrial stimulation at a coupling interval of 290 msec blocked in antegrade fashion in accessory pathway, conducted to ventricle with a right bundle branch block, and initiated paroxysmal supraventricular tachycardia during which activation of left atrium preceded activation of low and high right atrial sites. These findings are consistent with presence of left sided bypass tract. From top to bottom: right atrial electrogram (RA), His bundle electrogram (HBE), left atrial electrogram (LA), scalar leads I, II, III, and V, and stimulus channel (St.). Paper speed is 100 mm/sec; numbers indicate milliseconds. A = atrial potential, e = electrogram recorded at the site of stimulation, H = His bundle potential, V = ventricular potential. Of the paced beats, only the last in the basic train and the premature stimulus are displayed. (From Zipes DP, Gaum WE, Foster PR, Rosen KM, Delon W, Amat Y, Leon F, Noble RJ. Aprindine treatment of supraventricular tachycardias. With particular application to Wolff Parkinson White syndrome. *Am J Cardiol* 40:586, 1977.)

flutter from 1:1 conduction over the accessory pathway to 2:1 conduction over the normal pathway. In another patient, it slowed the ventricular rate during atrial fibrillation from 140 to 180 to 80 to 100 beats/min. Thus, eight patients had an excellent clinical response, but treatment with aprindine was discontinued in two patients. Electrophysiologic evaluation revealed that aprindine produced complete block or increased refractoriness of the accessory pathway in an anterograde direction in all patients and in a retrograde direction in all but two patients tested (Fig 1).

Our total current experience includes 152 patients treated with aprindine for a variety of tachyarrhythmias, including 130 patients with ventricular tachycardia (Fig 2), 13 patients with supraventricular tachycardia, four patients with premature ventricular complexes (PVCs), two patients with atrial fibrillation, and one patient with atrial tachycardia. Fifty-seven patients con-

tinue to receive aprindine (range 1 to 40 months) for ventricular arrhythmias (53 patients) and supraventricular arrhythmias (four patients). Reasons for discontinuing the drug include inadequate control of ventricular arrhythmias (50 patients) or exacerbation of ventricular arrhythmias (five patients). In two patients, the arrhythmia resolved and the drug was stopped in two patients for noncompliance. Fourteen patients discontinued aprindine because of side effects, and 13 patients died while receiving the drug, although in none was the drug implicated as a cause of death.

Side effects

The toxic therapeutic ratio for aprindine is rather narrow, and side effects, particularly during the initial loading period and adjustment of the maintenance dose, are common. These side

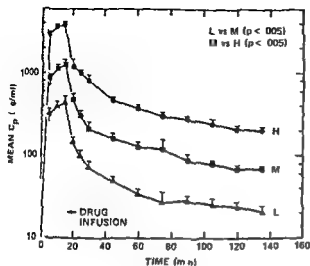


Fig 1 Plasma concentration (C_p) of encainide with time for high dose (H) of 27 mg/kg in seven dogs, medium dose (M) of 09 mg/kg in four dogs, and low dose (L) of 03 mg/kg in four dogs. The shaded area indicates the 15 minute period of drug infusion. Statistical intergroup differences were evaluated at the end of the infusion period. (From Sami M, Mason JW, Harrison DC. Canine electrophysiology of encainide: a new antiarrhythmic. *Am J Cardiol* 43:1149, 1979.)

Fig 1 Peak plasma concentrations averaged 415 ng/ml in Group 2, 1300 ng/ml in Group 3, and 4000 ng/ml in Group 4. The disappearance from plasma was fitted to a two-compartment pharmacologic model with linear kinetics.

Blood pressure was not altered at any dosage level throughout the study. Heart rate was insignificantly changed. The duration of the QRS complex was prolonged and could be related to the plasma concentration of the drug (Fig 2). H-V intervals were prolonged at all doses (Fig 2). The effects on H-V interval and QRS duration in relation to plasma concentration could be linearized when log plasma concentration was plotted against the change in electrophysiology produced by the specific agent (Fig 3). There was no significant change in heart rate, corrected sinus node recovery time, A-H intervals, QT intervals, or atrial A-V nodal or left ventricular refractory periods. We concluded that encainide was different from clinically available antiarrhythmic agents in that it prolonged His-Purkinje system conduction without significantly affecting conduction or refractoriness of other parts of the cardiac conduction system in animals.

With the completion of these studies and no documented specific adverse hemodynamic or electrophysiologic effects, we proceeded to study

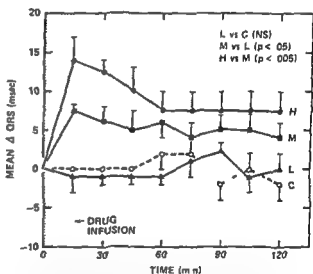
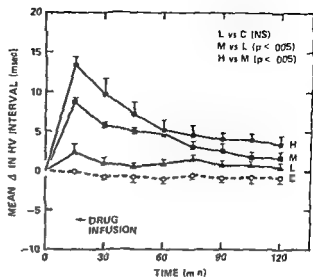


Fig 2 Temporal changes (Δ) in the mean H-V interval (top) and QRS duration (bottom) in five control animals (C) and four animals receiving a low (L) dose (03 mg/kg), four receiving a medium (M) dose (09 mg/kg), and seven receiving a high dose (H) (27 mg/kg) of encainide. Statistical intergroup differences were evaluated at the end of the infusion period (T). NS = not significant; P = probability. (From Sami M, Mason JW, Harrison DC. Canine electrophysiology of encainide: a new antiarrhythmic. *Am J Cardiol* 43:1149, 1979.)

the effects of encainide on ventricular fibrillation threshold, which has been used as a measure of the effects of an antiarrhythmic drug in preventing ventricular fibrillation.

We demonstrated a stepwise progressive increase in ventricular fibrillation threshold with progressively greater doses and plasma concentrations of encainide. These studies were per-

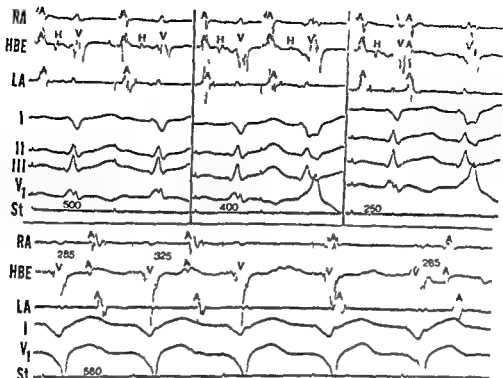


Fig 1B Complete antegrade and retrograde block in accessory pathway during administration of aprindine. Top panels display the last driven beat of the basic train and the premature right atrial stimulus delivered at coupling intervals of 500, 400 and 250 msec respectively. Both basic and premature beats are conducted to ventricles over the normal pathway, with a right bundle branch block similar to the contour of the QRS complex initiated during supraventricular tachycardia seen in Fig 1A. His bundle activation was slurred and delayed after premature stimulation at intervals of 500 and 400 msec; after premature stimulation at 250 msec a clear His bundle spike could not be recorded. Supraventricular tachycardia could not be initiated at any coupling interval. Bottom panel shows right ventricle being stimulated at a constant cycle length of 560 msec. Note that low right atrial activation preceded high right atrial activation and that the latter preceded left atrial activation. This sequence of retrograde atrial activation is entirely different from the corresponding sequence that occurred during supraventricular tachycardia seen in Fig 1A. Complete retrograde block in the accessory pathway is present. Note also that a retrograde Wenckebach block occurred in the normal pathway: the LA interval progressively lengthened culminating in LA block after the third QRS complex. The third P wave is probably a sinus initiated P wave. Conventions same as in Fig 1A. Same patient as in Fig 1A. (From Zipes DP, Gaum WE, Foster PR, Rosen KM, Delon W, Amat Y, Leon F, Noble RJ. Aprindine treatment of supraventricular tachycardias. With particular application to Wolff-Parkinson-White syndrome. *Am J Cardiol* 40:580, 1977.)

effects related to the dose and serum concentration of aprindine include most commonly a tremor of the hand and fingers. As the serum concentration increases, dizziness, intention tremor, ataxia, nervousness, hallucinations, diplopia, memory impairment, or seizures may also occur. Neurologic side effects are minimal or absent at serum aprindine concentrations of less than 1 µg/ml. Gastrointestinal side effects are more infrequent than neurologic side effects.

Recently, cholestatic jaundice and agranulocytosis have been reported to occur in association with the use of aprindine and are thought to be idiosyncratic reactions as opposed to dose-related toxicity. The problems have generally occurred

between the fourth and sixteenth weeks of aprindine therapy and with an estimated incidence of approximately one in several thousand based on data from Europe. In the United States of approximately 1,500 patients treated, 10 have developed agranulocytosis (WBC <500/ml). Eight patients recovered after aprindine was discontinued. One of these patients died of ventricular fibrillation 24 hours after discontinuation of aprindine. In addition, about one in every 30 patients has exhibited a WBC <1,500/ml. The majority of these patients had normal WBC counts subsequently in spite of continuing aprindine. Only one patient had aprindine discontinued because of a WBC <1,500/ml. It is possible

Table 1 Stanford studies with encainide

| Animal studies | Human studies |
|--|--|
| Basic electrophysiology in canine model | Basic electrophysiology with normal cardiac conduction |
| Encainide's effects on ventricular fibrillation threshold | Hemodynamic actions of encainide in normal and depressed ventricle |
| Action of encainide on monophasic action potential by endocardial electrode techniques | Single dose efficacy and pharmacokinetics in symptomatic ventricular arrhythmias |
| | Encainide in life threatening ventricular tachycardia |
| | Comparison of quinidine and encainide on arrhythmias late after infarction |
| | Safety and long term efficacy of encainide |

formed in an animal model in which lidocaine was demonstrated to increase the ventricular fibrillation threshold as a prototypical response. Specific examples of the increase in ventricular fibrillation thresholds as compared to control are illustrated in Fig 4.

Additional studies in animal models utilizing endocardial electrostimulation techniques for studying simulated action potentials from intact animal preparation were utilized for studying the cardiac effects of encainide. Dose and plasma concentration related effects on the slope of phase zero (dV/dt) of these endocardial action potentials were demonstrated together with moderate prolongation of the duration of the action potential. Detailed results of these studies are to be published.

Clinical electrophysiologic effects of encainide. Following the demonstration that encainide had important electrophysiologic properties in animals studies were carried out in patients undergoing electrophysiologic studies in the cardiac catheterization laboratory.* Standard His electrograms were recorded in 10 patients with coronary artery disease before and after the administration of encainide. Five patients were given 0.6 mg/kg and five patients 0.9 mg/kg intravenously during a constant infusion of 15 minutes duration. Plasma concentrations of encainide, heart rate, blood pressure and conduction intervals were measured before, during and after encainide infusion. In addition, sinus node recovery time, Wenckebach cycle length and atrial A-V nodal and right ventricular refractory periods were measured before and after the encainide infusion. The average peak plasma concentration was $0.49 \pm 0.35 \mu\text{g/ml}$ (mean \pm standard error of the mean) in the 10 patients studied.

Encainide significantly prolonged H-V and QRS intervals in all patients by an average of $31 \pm 7\%$ and $18 \pm 9\%$ SD ($P < 0.001$) respectively (Fig 5). An increase in the Q-T interval was also observed after encainide infusion ($2\% \pm 9\%$) but no significant changes were noted in heart rate, blood pressure, A-H intervals, corrected sinus node recovery time, Wenckebach cycle length, refractory periods of the atrium, A-V node or right ventricle. From these studies we concluded that encainide significantly prolonged conduction in the His-Purkinje system without markedly affecting conduction or refractoriness of other parts of the cardiac conduction system in man. No consistent hemodynamic effect was observed in the 10 patients included in this study. Significant correlation of the plasma concentration with the electrophysiologic effects was observed.*

Single dose efficacy and pharmacokinetics. In order to evaluate the pharmacokinetic and single dose efficacy of encainide, nine hospitalized patients with frequent and complex ventricular premature beats were studied in a 3 day double blind protocol. Each day patients received either encainide 75 mg intravenously, encainide 75 mg orally, or an appropriate placebo. Frequent plasma samples for encainide concentration were taken and continuous ambulatory electrocardiograms recorded.¹

Eight of the nine patients were documented to have antiarrhythmic effects due to encainide (Fig 6). The inclusion of a placebo day provides a control against attributing spontaneous variation of premature ventricular contraction (PVC) frequency to encainide's antiarrhythmic effects. The duration of continuous 90% or greater suppression of PVCs after intravenous encainide ranged from 5 to 36 hours. The antiarrhythmic efficacy of

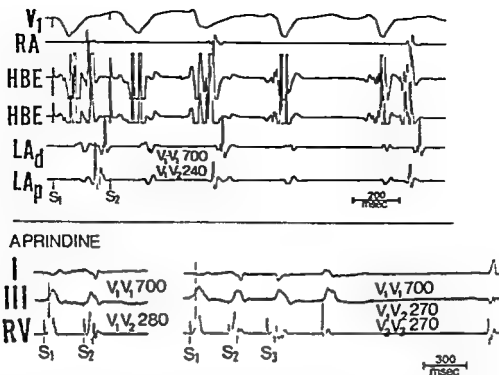


Fig 2 Initiation of ventricular tachycardia (top panel) during premature right ventricular stimulation at interval of 240 msec. After aprindine administration (bottom panel) only a single spontaneous ventricular extrasystole followed two premature ventricular stimuli. LA_d = left atrium near appendage LA_p = left atrium near septum, recorded with a catheter passed across a patient's foramen ovale

that all of these cases of leukopenia were not related to aprindine. Transient abnormalities in liver function tests have been noted in some of our patients but no abnormality has persisted or has led to discontinuation of the drug.

Clinical pharmacology

Aprindine is well absorbed, has high systemic availability, and is 85% to 95% protein bound. Approximately 90% of the hydroxylated metabolites undergo glucuronidation in the liver. Sixty-five percent of aprindine and its metabolites is found in the urine, with the remaining 35% in the feces. Elimination half-life has ranged from 13 to 50 hours (mean 27 hours) in one study, 20 hours to 30 hours in another, and 18 hours (mean) in a third.¹⁷ The *N*-desethyl metabolite is present in small amounts in the plasma of patients treated chronically with aprindine and exerts some antiarrhythmic actions. Clinically, the full antiarrhythmic effect of aprindine may not occur for several days, even when the drug is initially administered in a loading dose.

Hemodynamic studies have revealed that therapeutic doses of aprindine mildly depressed myo-

cardial function. In man, aprindine (200 mg orally) slightly decreased systolic and mean aortic blood pressure during exercise in one study¹⁸ and slightly depressed myocardial contractility when given intravenously (100 mg) in another. At a total dose of 140 or 150 mg intravenously, aprindine produced a moderate and dose-related decrease in peak left ventricular dP/dt and V_m.¹⁹

Electrophysiology

In isolated cardiac preparations, aprindine shortened the duration of the action potential and effective refractory period of Purkinje fibers; the former was shortened more than the latter.²⁰ However, in cardiac muscle fibers, action potential duration was only slightly reduced and the duration of the effective refractory period was lengthened. The rate of rise of phase 0 was depressed more so at rapid rates at higher potassium levels and to a greater degree than with comparable amounts of lidocaine.²¹ Diastolic depolarization and spontaneous firing were depressed or abolished by aprindine. Aprindine also reduced digitalis-induced increases in potas-

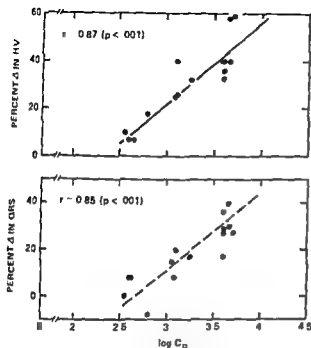


Fig 3 Linear regression of the change in (Δ) of the HV interval and the QRS duration and the log plasma concentration (C_p) of encainide at the end of a 15 minute infusion for all 15 animals in this study. P = probability r = correlation coefficient (From Sami M. Mason JW. Harrison DC. Canine electrophysiology of encainide: a new antiarrhythmic. *Am J Cardiol* 43:1149-1979)

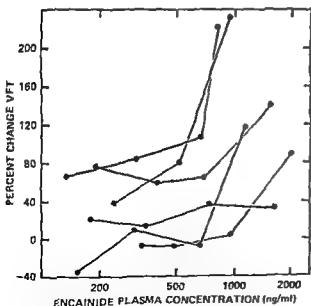


Fig 4 Percentage of increase in ventricular fibrillation threshold (VFT) in relation to plasma concentration for encainide for six dogs.

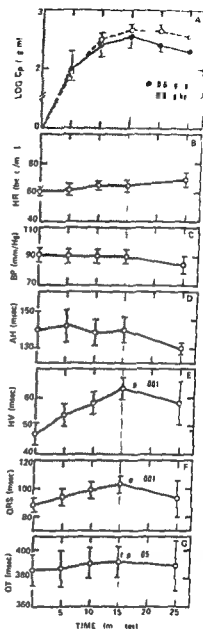


Fig 5 Comparison of temporal changes in selected measurements made during constant base atrial pacing. In panel A data for the five patients given 0.6 mg/kg and the five patients given 0.9 mg/kg of encainide are plotted separately. In panels B through G the data are combined for the two groups. Mean values (open circles) \pm standard error of the mean (bars) are plotted at time 0 (control), during encainide infusion (shaded area) and after encainide infusion (15 to 25 minutes). From top to bottom: C_p = plasma concentration of encainide; HR = heart rate; BP = mean aortic blood pressure; AAI interval; HV interval; QRS duration; QT interval. Significance levels were measured at end of infusion ($t = 15$ minutes). $P < 0.001$. $P < 0.01$. Bars indicate standard deviation. (From Sami M. Mason JW. Leters F. Harrison DC. Electrophysiologic effects of encainide: a newly developed antiarrhythmic. *Am J Cardiol* 44: 6-1979)

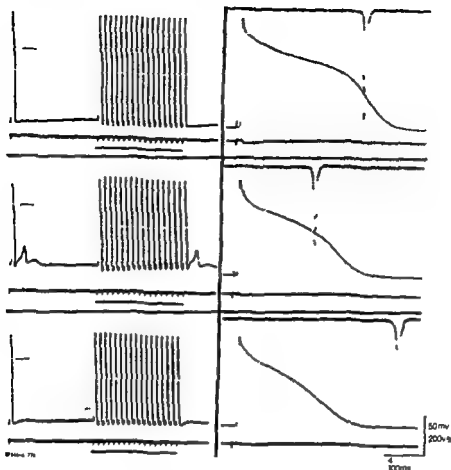


Fig 3 Effect of aprindine (3×10^{-4} M) on transient depolarization induced by acetylcholinesterase (1.7×10^{-4} M). From top to bottom the traces of each panel in the left hand column represent the transmembrane action potential, the bipolar electrogram and the stimulation period (8 sec) at a cycle length of 500 msec. In the right hand column the traces represent (from top to bottom) the dV/dt of the upstroke, the transmembrane action potential and the bipolar electrogram. Upper panel: Control recording. Middle panel: After 32 minutes of superfusion with acetylcholinesterase (1×10^{-4} M). Lower panel: Nine minutes after superfusion with aprindine (3×10^{-4} M). All recordings were obtained from the same impalement. (From Elharrar V, Bailey JC, Lathrop DA, Zipes, DP. Effects of aprindine HCl on slow channel action potentials and transient depolarization in canine Purkinje fibers. *J Pharmacol Exp Ther* 205:410-1978.)

sum permeability' and suppressed transient depolarizations caused by acetylcholinesterase in canine Purkinje fibers (Fig 3).³⁰ Aprindine does not appear to affect slow channel activity of canine Purkinje fibers at concentrations of 3×10^{-6} to 1×10^{-4} M (Fig 4).

The effects of aprindine on transmembrane currents in frog (*Rana ridibunda*) atrial trabeculae have been studied by means of a voltage clamp technique. Aprindine (1×10^{-4} gm/ml) reduced maximum inward sodium current by $38.6 \pm 7.2\%$ (mean \pm SEM, $n = 6$) but had no effect on the slow inward current or outward current. A higher dose of aprindine (2.8×10^{-4}

gm/ml) suppressed both the fast inward current and the slow inward current. Aprindine (2.8×10^{-4} gm/ml) also depressed slow channel dependent membrane oscillations induced in atrial trabeculae by injection of current pulses. These data indicate that aprindine possesses fast and slow channel blocking properties in the frog, the latter being more apparent at high concentrations of the drug.

Studies in intact dogs have revealed that aprindine injected into the sinus nodal artery decreased the spontaneous sinus rate and injected into the A-V nodal artery, prolonged the functional refractory period and conduction time

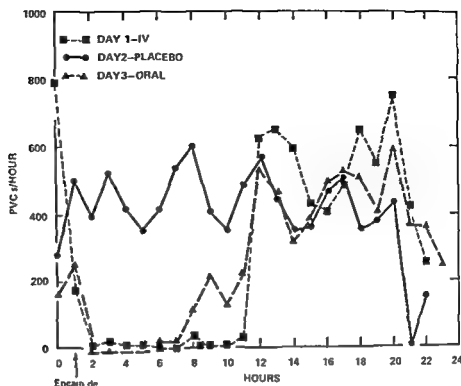


Fig 6 Premature ventricular contraction (PVC) frequency per hour response to placebo (●) oral encainide (Δ) and intravenous encainide (■) in a patient with frequent and symptomatic PVCs.

Table II Encainide pharmacokinetics in nine subjects (mean \pm SEM)

| Pharmacokinetics | Results |
|--|-----------------------------------|
| Half life (hr) | |
| Intravenous | 338 \pm 056 (mean \pm SEM) |
| Oral | 247 \pm 096 |
| Bioavailability (%) | 419 |
| Clearances (ml/min/kg) | 132 \pm 187 |
| Antiarrhythmic offset plasma concentration (ng/ml) | |
| Intravenous | 390 \pm 193 |
| Oral | 1496 \pm 373 |

encainide in these studies following oral administration was equal to that of intravenous administration. Following oral administration the duration of effect was greater in most patients than for the intravenous administration suggesting the presence of an active metabolite. In several patients a new high pressure liquid chromatography (HPLC) assay was used to detect these metabolites (Fig 7). The kinetics and physiologic action of these metabolites are now under further study.

Pharmacokinetic studies demonstrated a

marked intersubject variation in bioavailability (mean $42 \pm 24\%$) clearance ($132 \text{ ml} \pm 56 \text{ ml/min/kg}$) and half life (34 ± 17 hours intravenously 25 ± 08 hours orally) (Table II). Minimal antiarrhythmic plasma concentration was higher ($39 \pm 54 \text{ ng/ml}$) after intravenous dosing than after oral dosing ($14 \pm 16 \text{ ng/ml}$) suggesting an active metabolite after oral dosing in many of the patients. Minimal side effects were seen despite high peak plasma concentration (range 794 to 1556 ng/ml intravenously 36 to 495 ng/ml orally). The minimal ratio of toxic to therapeutic plasma concentration ranged from 4.3 to 326 with a median value of 27 after oral dosing. Antiarrhythmic action was associated with 11% to 44% widening of the QRS complex which did not correlate with any other adverse side effects seen. From these studies we believe that encainide is a highly effective agent for suppressing ventricular arrhythmias. In spite of a wide range of bioavailability, high plasma clearance and relatively short half life, its wide toxic to therapeutic ratio and the existence of an active metabolite permits a long duration of action that should allow a reasonable dosing schedule in most patients by the oral route.¹⁰

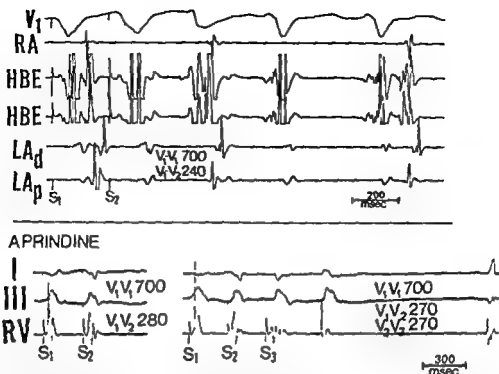


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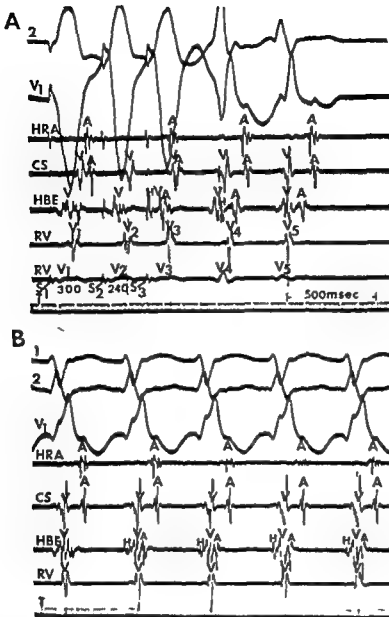


Fig 2 Initiation of intraventricular reentry and relationship to spontaneous arrhythmia. ECG Leads 2 and V₁ are shown with electrograms from the high right atrium (HRA), coronary sinus (CS), His bundle (HBE), and right ventricle (RV). In panel A, after the eighth paced ventricular complex (S₃), two premature stimuli (S₄ and S₅) are introduced at coupling intervals of 300 (S₄ S₃) and 240 (S₅ S₃) msec. S₄ results in two extra ventricular responses (V₄ and V₅) which are not preceded by His potentials and which have a bundle branch block morphology, and are due to intraventricular reentry (IVR). The patient's spontaneous ventricular tachycardia shown in panel B has a similar configuration and intracardiac activation pattern as the IVR. Note "wandering" retrograde His potentials (H) during the tachycardia.

Impulses were 10 msec in duration and were twice diastolic threshold (≤ 3 mA). The stimulation protocol included ventricular pacing at control cycle lengths ranging from 500 to 1000 msec during which single and/or double ventricular extrastimuli were delivered after every eighth paced complex. The ventricular extrastimuli were delivered at progressively premature coupling

intervals until ventricular refractoriness was reached.

Definition of terms

S₁–S₁ was the basic paced cycle length.
S₁ and S₂ were the first and second premature stimuli delivered during an S₁ S₁.
S₂ S₁ was the coupling interval between the

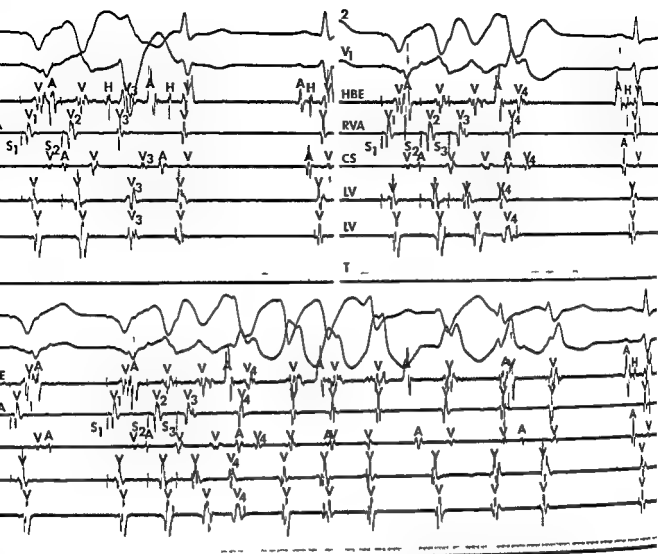


Fig 3 Bundle branch reentry and intraventricular reentry in the same patient. The figure is organized from top to bottom: surface electrographic Leads 2 and V₁ and intracardiac electrograms from His bundle (HBE), right ventricular apex (RVA), coronary sinus (CS), two electrograms from left ventricle (LV) and time lines (T). In the upper left panel, an RV extrastimulus (S₂) delivered at a coupling interval of 250 msec during ventricular pacing at a cycle length of 600 msec (S₁ S₂) results in a bundle branch reentrant complex (V₂). In the upper right panel, a second RV extrastimulus (S₃) is delivered at a coupling interval of 180 msec. Bundle branch reentry is abolished but a repetitive response (V₄) due to intraventricular reentry (IVR) results. Note the difference between the IVR and paced complexes. In the lower panel, ventricular stimulation similar to the upper right panel results in an IVR identical to the one above, followed by a short run of ventricular tachycardia. Note the similarity between the configuration of the IVT and ventricular tachycardia complexes.

length impulse of the basic drive cycle length to the first premature stimulus.

S₁ S₂ was the coupling interval between the first and second premature stimuli.

V₁, V₂, V₃ were the ventricular depolarizations produced by S₁, S₂ and S₃ respectively.

Repetitive ventricular responses were defined as single or multiple ventricular complexes that were reproducibly induced by S₁ or S₂. Early responses due to AV nodal reentry were not

considered as repetitive ventricular response. Two types of repetitive ventricular response were noted: bundle branch reentry and intraventricular reentry (Figs 1 and 2). Bundle branch reentry was recognized by the appearance of an extra nonstimulated ventricular depolarization in response to S₁ or S₂, which was dependent upon achieving a critical degree of retrograde His-Purkinje conduction delay (VH prolongation). The QRS of this type of reentrant response

tion. IZ aprindine concentrations were initially less than 15% of NZ aprindine concentration and increased with time to approach half of NZ aprindine concentration 70 minutes after LAD occlusion. Border zone aprindine concentrations were intermediate between NZ and IZ concentrations (Fig 5). Seventeen of 35 dogs (49%) receiving aprindine before LAD occlusion experienced sustained ventricular tachycardia or ventricular fibrillation compared to 5 of 34 (14%) receiving aprindine immediately after LAD occlusion ($P < 0.01$). 1 of 10 (10%) undergoing LAD occlusion without receiving aprindine ($P < 0.05$) and 0 of 16 receiving aprindine without LAD occlusion ($P < 0.01$). Aprindine administered 24 hours after coronary occlusion reduced PVCs from a mean of 35 to 12/100 beats ($P < 0.01$). The results of these studies¹⁰ indicate that the temporal relationship between aprindine administration and LAD occlusion importantly modifies the regional myocardial distribution of aprindine and its effects on ventricular arrhythmias after coronary artery occlusion.

Studies in man have demonstrated that aprindine increased the A-H and H-V intervals and QRS duration increased the effective refractory period of the atria and ventricles and increased the functional and effective refractory period of the A-V node.¹¹⁻¹³

We wish to thank Georgia Duncan for help in compiling the clinical data and Shirley Proffitt for secretarial assistance.

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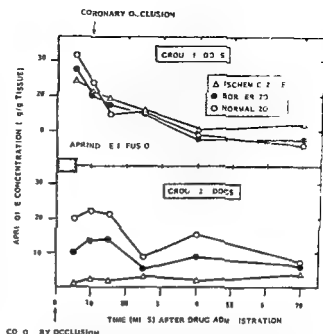


Fig 5 Regional myocardial aprindine concentrations among dogs of group 1 (given aprindine prior to coronary artery occlusion) and group 2 (aprinidine after coronary artery occlusion) as a function of time after the onset of aprindine infusion. Among group 2 dogs the differences between ischemic border and normal zone aprindine concentrations were all significant ($P < 0.01$).

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ing that verapamil has little or no effect on the rapid sodium and potassium transcellular fluxes

Clinical applications

Intravenous verapamil has several important clinical applications and may be used for the following conditions (1) the treatment of coronary artery spasm (2) the treatment of hypertensive crises and (3) the treatment of supraventricular tachyarrhythmias. It has also been used for such noncardiac conditions as relaxation of the uterus in threatened abortion and premature labor.²

Treatment of coronary artery spasm There are many causes of ischemic heart disease. A mechanism that has received increasing emphasis and recognition during recent years is coronary artery spasm. The recognition of this mechanism has in part been due to the increasing sophistication of available techniques for demonstrating such spasm. Thus coronary artery spasm is being increasingly recognized as a cause of the variant form of angina pectoris—Prinzmetal's angina,³ and its potential role in the enigma of sudden death has become especially important.⁴ It is interesting to note that Heberden postulated the mechanism of coronary artery spasm as early as 1768 and such medical giants as Osler⁵ and Gallavardin⁶ echoed this in later years. Clearly then, the advent of an important coronary spasmolytic agent is thus particularly important and especially so in the present day, coronary milieu where palliative surgical coronary artery bypass is becoming an all too frequent event.

The frequency of coronary artery spasm has recently received special emphasis through the elegant studies of Maseri et al.⁷ by means of continuous ECG and hemodynamic monitoring they documented 8 000 to 9 000 episodes of transient acute myocardial ischemia. These were reflected by ST-segment elevation or depression and T wave changes. The ECG changes occurred within minutes of the onset of pain but could also occur in the absence of pain. They also showed that spasm could occur in apparently normal coronary arteries and lead to ST-segment elevation to be followed shortly thereafter by deeply inverted T waves. During the phase of T wave inversion these patients usually developed ventricular tachycardia which sometimes progressed

to ventricular fibrillation and sudden death. The only way these episodes of ventricular fibrillation could be prevented was by treating the symptom, i.e. the relief of the vasospastic angina pectoris and not by the administration of antiarrhythmic drugs. They conclude that "preventing angina meant preventing ventricular fibrillation in these cases." This observation is of particular significance since it heralds an entirely new therapeutic approach. And in this respect verapamil is highly effective by both the oral route⁸ and the intravenous route⁹ in abolishing ameliorating and preventing coronary vasospastic attacks as reflected by angina of effort, angina at rest and in particular Prinzmetal's angina.

Treatment of hypertensive crises Hypertensive crises respond dramatically to the administration of intravenous verapamil.¹⁰ Blood pressure control is usually achieved within 1 to 2 minutes following the intravenous injection of 5 mg of verapamil. The effect is due to a reduction in peripheral vascular resistance and is in no way related to any negative inotropic effect. In this respect it is important to note that intravenous verapamil does not reduce normal blood pressure or at most has only a negligible and unimportant effect.

Treatment of supraventricular tachyarrhythmias Intravenous verapamil was first used for the treatment of arrhythmias in the late 1960s and my experience with this agent both on an investigational basis and in routine clinical practice now involves many hundreds of cases and extends over a decade. Most of these patients had grade IV cardiac failure and received digitalis therapy. This experience has left me with no doubt whatsoever that verapamil is the best available pharmacologic agent for rapid action in affecting A-V nodal delay or block. This property is of particular value in interrupting the conduction circuit of a reciprocating tachycardia and thereby terminating the attack. Note that it makes no difference which anatomic bypass is used in the reciprocal circuit—a James bypass, an intranodal pathway, a Kent bundle or a Mahaim fiber—since termination is effected by block with in the A-V nodal part of the circuit and not within the bypass.

The Investigators Brochure of the Knoll Pharmaceutical Company reflects a review of 134 studies involving the use of intravenous verapamil.

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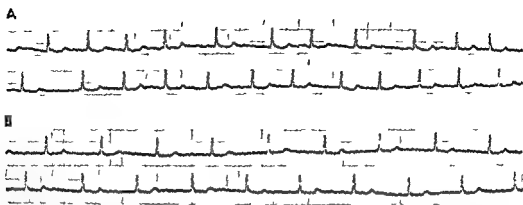


Fig 1 A Section of the control tracing (continuous strip of standard lead II) showing atrial fibrillation with irregular ventricular response B Tracing recorded after the administration of intravenous verapamil shows regularization of the ventricular response

nul for the treatment of various arrhythmias. There were 4 379 documented arrhythmic episodes treated with intravenous verapamil, some of which are considered in further detail below.

Supraventricular tachycardia The Knoll review reflects 1 607 published episodes of supraventricular tachycardia treated with intravenous verapamil. Of these 1 307 (81%) were converted to normal sinus rhythm and 139 (9%) reflected a significant reduction in rate. The precise mechanism of the supraventricular tachycardia, however, was not always certain and no distinction in this analysis could therefore be made between ectopic atrial supraventricular tachycardia and reciprocating tachycardia. Such distinction, however, is very important in the evaluation of this drug. Thus, my experience comprises 59 cases of the reciprocating form of supraventricular tachycardia. Eighteen of these cases involved retrograde conduction through a Kent bundle; one was associated with anterograde conduction through a Kent bundle and two were associated with retrograde conduction through a Mahaim fiber. The precise anatomic substrate for the circus movement could not be determined in the remaining 38 cases, although the diagnosis of reciprocating tachycardia was clear. The reciprocal circuit could have involved an intranodal bypass, a James bypass, or retrograde conduction through a Kent bundle or Mahaim fiber. The reciprocating tachycardia was terminated with conversion to normal sinus rhythm in all 59 cases (100%).

Atrial flutter The Knoll review reflects 343 documented episodes of atrial flutter treated with

intravenous verapamil. Of these 31% were converted to normal sinus rhythm and a significant reduction of the ventricular response was obtained in 186 (54%). My experience comprises 87 patients with atrial flutter, all of whom had a reduction in ventricular response. Thirteen (15%) of these subsequently converted to normal sinus rhythm. Eleven (13%) converted to atrial fibrillation, two of which subsequently converted to normal sinus rhythm.

Atrial fibrillation The Knoll analysis reflects a total of 1 474 documented episodes of atrial fibrillation treated with intravenous verapamil. Of these 230 (16%) were converted to normal sinus rhythm and a significant rate reduction was obtained in 1 149 (78%). The data include my own investigational experience of 115 cases. Of these 115 cases, a reduction in ventricular response was obtained in 111 (97%). The higher the initial control rate, the higher the ensuing reduction following the administration of intravenous verapamil. There was also a diminution in the amplitude of the fibrillating deflections in 44% of cases. In contrast to other studies in which conversion to sinus rhythm was obtained in a moderate number of cases, there was no conversion to sinus rhythm in the studies of Schamroth et al.¹¹ A possible reason for this was the advanced state of disease and the marked associated cardiomegaly in most of these patients.

A noteworthy feature was an associated regularization of the ventricular response in most of these patients. This occurred in the presence of continuing atrial fibrillation and in the absence of complete A-V block* (Figs 1 and 2).

Amiodarone in the treatment of cardiac arrhythmias in children One hundred thirty five cases

Philippe Coumel MD and Jean Fidelle MD *Paris and Les Loges-en-Josas France*

Oral amiodarone was given to 135 children (mean age 10.2 years) for a mean duration of 4.1 months (range 1 day to 8 years) for mainly idiopathic (25%) and postoperative (61%) arrhythmias. Complete ECG control or partial ECG control with clinical improvement was obtained in 60% and 33% of cases respectively regardless of the arrhythmia location (atrial 69%, junctional 16% and ventricular 15%) mechanism (resistance 55%) or sensitivity (45%) to other drugs and presence of cardiomegaly (40%) or clinical signs of heart failure (27%). The only factor favoring improvement was a short history (< 2 months in 54%). The rapid onset of drug effect (4.1 days), the early relapses after treatment discontinuation (3.3 weeks) and the absence of side effects due to drug accumulation reflect a faster metabolism than that in adults with no cardiac toxicity and a low incidence of thyroid dysfunction (2% hyperthyroid, 1% hypothyroid).

Two factors are responsible for the greater difficulty in treating arrhythmias in children compared to adults: (1) the many different types of arrhythmias, some of which are refractory and peculiar to children and (2) the limitations of therapeutic choice due to greater drug toxicity. This is why amiodarone is a considerable therapeutic asset in children. We report here our experience since 1971.

Material and methods

The study includes 135 children (80 boys and 55 girls), ages 0 to 15 years (Fig 1) treated and followed up from 1971 to 1979 and also includes a previously published study¹ of 50 patients. The diagnosis and cause of the arrhythmias are detailed in Tables I and II. The predominance of atrial (69%) and postoperative arrhythmias (61%) is emphasized, as well as some resistant arrhythmias such as permanent reciprocal tachycardia², congenital ectopic His bundle tachycardia³ (Figs

2A and 2B) and catecholamine ventricular tachycardias (Fig 3).

The arrhythmias were accompanied by clinical cardiac failure in 27%, isolated radiologic cardiomegaly in 40% and were well tolerated hemodynamically in only 33% of the cases. The arrhythmias were chronic (lasting more than 2 months) in almost half of the cases (46%). In over half (55%) the arrhythmias were resistant to the various antiarrhythmic drugs used in children, i.e. digitalis, disopyramide, beta blockers, atropine and verapamil. Among the remaining patients, some had no treatment other than amiodarone because they had well known resistant arrhythmias.

The initial treatment was a daily oral dose of 800 mg of amiodarone adjusted according to the child's surface area. This dose was maintained for an average of 2 weeks, then reduced by half and was finally given 5 days out of 7. Because of our adult experience and the large predominance of supraventricular arrhythmias, most of the patients were also digitalized. Digitalization was always achieved before amiodarone was given in cases of cardiac failure and was associated with a diuretic. In a small number of cases (eight patients), one single dose of amiodarone was given

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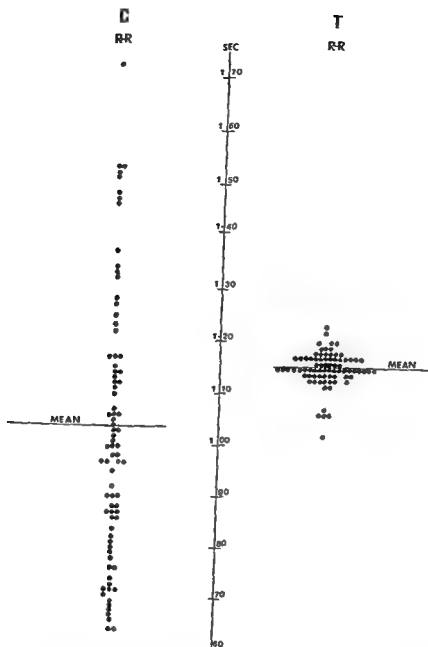


Fig 2 ~ with the "regularization" of the ventricular rhythm. C = scatter of the R-R intervals in the control tracing; T = scatter of the R-R intervals in the second test tracing.

The mechanism of the regularizing effect is uncertain. It is unlikely to be due to the development of complete A-V block with A-V nodal escape rhythm since the escape rhythm is too fast and some irregularity will still present. It may result from a stabilizing effect on the varying degrees of concealed A-V nodal conduction which may cause the irregular ventricular

response in atrial fibrillation—perhaps by increasing the absolute but not relative refractory period. An activation front approaching the atrioventricular node from the direction of the SA node is well transmitted whereas a front approaching from other directions may be delayed or blocked. Verapamil may stabilize the chaotic atrial activation front.

No cases

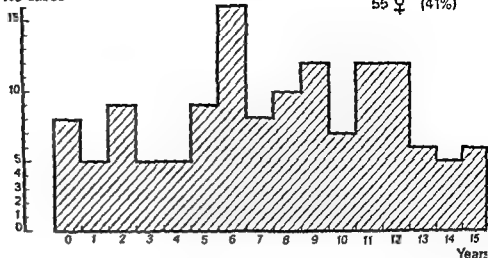


Fig 1 Age and sex distribution of the 135 patients

Table I Arrhythmia diagnosis (n = 135)

| Type | No of cases | % |
|---|-------------|-----|
| <i>Atrial</i> | 7 | 5 |
| Sinus tachycardia | | |
| Coronary sinus rhythm | 1 | 1 |
| Extrasystole | 31 | 23 |
| Ectopic tachycardia | 43 | 32 |
| Flutter fibrillation | 4 | 3 |
| Bradycardia tachycardia syndrome | 7 | 5 |
| Total | 93 | 69% |
| <i>Junctional</i> | 7 | 5 |
| Permanent reciprocating tachycardia | | |
| Paroxysmal reciprocating tachycardia (WPW) | 8 | 6 |
| His tachycardia | 7 | 5 |
| Total | 22 | 16% |
| <i>Ventricular</i> | 15 | 11 |
| Extrasystole | | |
| Ventricular tachycardia | 1 | 1 |
| Catecholamine induced ventricular tachycardia | 4 | 3 |
| Total | 20 | 15% |

WPW = Wolff Parkinson White syndrome

Table II Etiology of arrhythmias

| Etiology |
|--------------------------------|
| Idiopathic |
| Congenital cardiopathies |
| Preoperative |
| Postoperative |
| Wolff Parkinson White syndrome |
| Valvular diseases |
| Cardiomyopathies |

controls many of which had at least one episode of arrhythmia at normal recording speed with stimulation and then at double these rates. The effect of the drug was usually evident on the slow recording and was progressively more evident with longer term treatment in nonhospitalized patients.

The mean treatment period was 1.5 years (range 1 day to 6 years). For long-term treatment the follow-up included monitoring of psychomotor development, weight, and serum levels to detect liver dysfunction (cholesterol and Hamolsky test).

Results

The results were considered good when the sinus rhythm was reestablished and the heart rate was reduced but the arrhythmia was not perfectly controlled on the long-term treatment when the treatment clinically and

to terminate attacks of supraventricular tachycardia and the treatment was discontinued after it was successful. We have no experience with the intravenous route in childhood.

The rate monitoring was a follow-up based on heart rates taken every 2 hours during the day and night and included several daytime and nighttime ECG

This regularization effect has recently also been noted following the administration of large doses of oral verapamil¹

Ventricular tachycardia The Knoll analysis reflects a total of 239 documented episodes of ventricular tachycardia treated with intravenous verapamil. Of these 239 episodes 157 (66%) were apparently converted to normal sinus rhythm. This contrasts with my own experience in which no effect was noted in ten cases of extrasystolic ventricular tachycardia and I have stopped using verapamil for this purpose. This difference in experience may be due to the fact that here again the precise mechanism of the ventricular tachycardia was delineated. Thus for example an idioventricular tachycardia will be abolished if its rate is slowed relative to the sinus rate. Extrasystolic ventricular tachycardia will not be affected in this way.

Contraindications

Verapamil is a safe drug provided certain basic contraindications are heeded. The drug should not be administered under the following circumstances: cardiogenic shock, any degree of A V block, structural nodal disease (the so called sick sinus syndrome), hypotension (except where due to a tachyarrhythmia as such) and in association with beta blocking agents or disopyramide.

Comments Verapamil should also be used with caution in the presence of intraventricular conduction defects.

The so called sick sinus syndrome is an unfortunate term for it is abundantly clear that it is not only the sinus node which is so to speak sick but also the A V node and its appendages. Structural nodal disease is preferred since it connotes a widespread disease process involving the conducting system. Verapamil is contraindicated when any manifestation of this syndrome is evident.

The negative inotropic effect Verapamil has a slight negative inotropic effect which is usually insignificant. This is more than counterbalanced by the reduction in the peripheral resistance and the reduction in cardiac work resulting from the diminution in the afterload as indicated by Ferlinz et al.

The question of adverse side effects

I have had no deaths or adverse effects in any of my patients. Four deaths following the adminis-

tration of verapamil have been reported in the world literature. The circumstances in all these cases however were either bizarre and/or clear contraindications were present. Thus (1) The case reported by Sacks and Kennelly² was that of a 63 year old man in cardiogenic shock and who also had bifascicular block. (2) The case reported by Witchitz et al³ was a 63 year old woman with sarcoma of the heart. (3) The case reported by Apitz and Gaismarer⁴ was that of a 10 year old boy with fibroelastosis who had first to third degree A V block. (4) The case reported by Heck et al⁵ was that of a 57 year old man who was seriously ill with myocardial infarction and in whom digitalis and verapamil were administered intravenously within a few minutes of each other.

Conclusions

Verapamil the pioneer of calcium ion antagonists represents an important milestone in clinical therapy. Its present status in cardiologic practice is that of significant benefit in three important conditions.

It stabilizes and slows or blocks conduction in the A V node and is the drug of choice for action on this structure. It has an important coronary spasmolytic action where its full potential has not as yet been realized. Its reduction of peripheral vascular resistance is important in the treatment of hypertension. And intravenous administration is of particular value in dealing with crises related to these situations. The reduction in cardiac afterload also has a beneficial effect on the ailing heart.

The future will see expansion of clinical application to other clinical disciplines where smooth muscle relaxation is the therapeutic aim. Verapamil thus heralds an exciting new era a new dimension in therapeutic approach.

I wish to thank the Photographic Unit Department of Medicine University of the Witwatersrand for the photographic reproductions.

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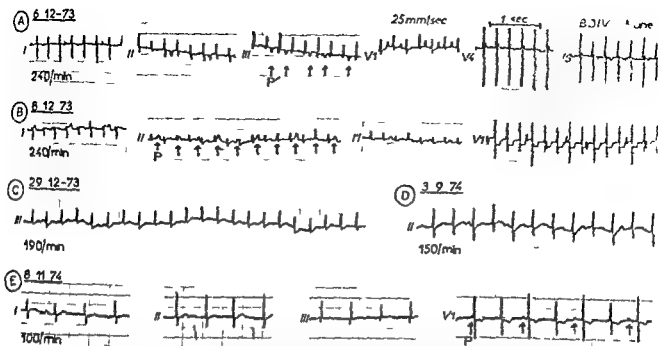


Fig 2A Resistant His bundle tachycardia in a 1 month old infant. The cardiac insufficiency (see Fig 2B) is clearly related to the supraventricular tachycardia in this infant: a cousin of whom died several years earlier from the same tachycardia after all antiarrhythmics had failed (amiodarone had not been tried). Tracing A (Dec 6 1973) clearly shows the narrow QRS complexes with a second degree ventriculoatrial block (arrows point to retrograde P waves). Two days later (tracing B) the A-V dissociation is complete. Tracings C to E were taken during the following 11 months and show the progressive slowing of the ectopic focus with a persistent A-V dissociation.

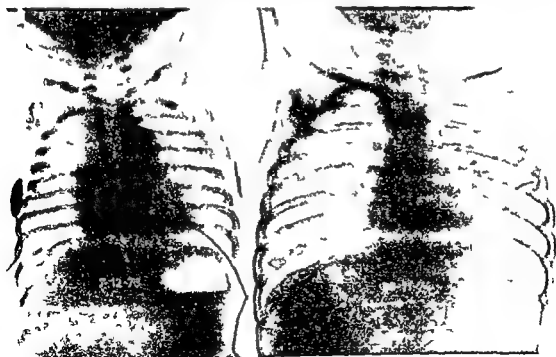


Fig 2B Dramatic regression of the cardiomegaly with the progressive slowing of the tachycardia in patient in Fig 2A. This case is classified as an average result (clinical but no ECG control of the arrhythmia).

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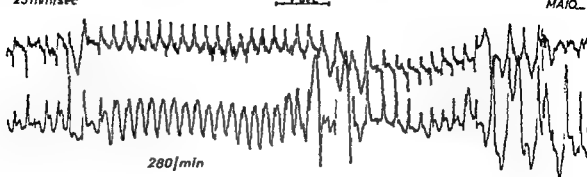


Fig 3 Catecholamine related severe ventricular tachycardia in an 8 year old boy. A strip from the Holter monitoring clearly shows the mechanism of the Adams Stokes syndrome: very rapid and polymorphic attacks of ventricular tachycardia and fibrillation are readily induced by exercise. Beta blockers were only partially effective and a new 6-year treatment with amiodarone did control the arrhythmia.

TIMING OF EFFICACY OF AMIODARONE TREATMENT

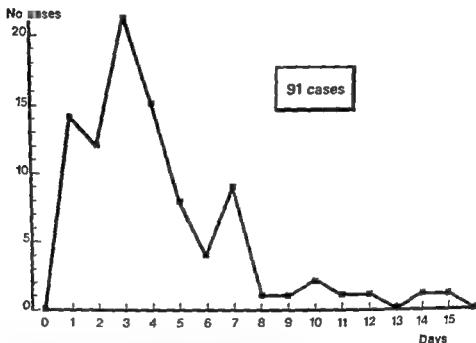


Fig 4 Delay before response to amiodarone treatment. In 91 patients in whom the delay could be precisely evaluated, the great majority (83) responded during the first week of treatment (one fourth at the third day). This is in contrast to the necessary 7 to 10 day impregnation in adults.

graphically was ineffective. The results were good in 81 cases (60%), average in 44 (33%) and poor in only 10 (7%), i.e. more than 90% of the cases totally or partially improved. The cause of the arrhythmia, its mechanism (ectopic focus or reentry), localization (Table III) and resistance to other antiarrhythmics (Table IV) do not affect drug efficacy (Pearson chi square test), although a longer duration of the arrhythmia (greater than 2 months) resulted in less drug effectiveness ($P < 0.10$).

The delay before response to treatment could be evaluated in 91 patients and is represented in Fig 4. It ranges from 1 to 16 days and its mean value is 4.1 days with a peak at day 3. In eight cases of supraventricular tachycardia a full single dose of oral amiodarone was given and rhythm reduction was obtained between 5 and 7 hours in seven patients and after 24 hours in one.

Conversely, the delay before relapses after interruption of treatment could be assessed in 3 cases of serious chronic and recurring arrhythmia.

V Other antiarrhythmic studies

Hemodynamic and electrophysiologic interactions between antiarrhythmic drugs and beta blockers, with special reference to tocainide

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The administration of beta receptor blocking drugs and antiarrhythmic drugs in close proximity may result in hemodynamic, electrophysiologic or pharmacokinetic interactions. We examined the hemodynamic and electrophysiologic effects of 0.20 mg/kg intravenous metoprolol followed by a 15 minute infusion of 0.75 mg/kg/min tocainide. In the six patients studied, metoprolol produced a fall in cardiac rate and output which was not further altered by tocainide. Both drugs decreased peak left ventricular (LV) dP/dt , ejection fraction, and mean V_t . There was no change in LV end-diastolic pressure or echo dimension and in clinical ill effects. In eight patients without sinus or A/V nodal disease, electrophysiologic studies showed mild depression of A/V conduction by metoprolol. Tocainide depressed sinus node function and shortened the functional refractory period of the His-Purkinje system. There were no clinical sequelae. However, three patients with preexisting electrophysiologic abnormalities developed asystole. There was no evidence of pharmacokinetic interaction. It is concluded that metoprolol and tocainide can be given concurrently with reasonable safety to cardiac patients without electrophysiologic abnormalities.

Antiarrhythmic drugs are frequently given concurrently with beta-adrenoreceptor drugs prescribed for angina, hypertension or arrhythmias. Such combinations may result in serious adverse effects from drug interactions. There are of three types.

First, there is hemodynamic interaction. This was exemplified by the development of circulatory collapse after intravenous verapamil had been given to a patient already on propranolol.¹ Another patient in this series with Wolff-Parkinson-White syndrome developed cardiogenic shock when propranolol was added to the verapamil therapy which was already being administered. Seabra-Gomes et al. showed that when intravenous practolol and verapamil were given individually to patients whose heart rates had been fixed with atrial pacing, there was little hemodynamic alteration. However, the adminis-

tration of the two drugs together resulted in a pronounced fall in cardiac output. They advise caution in the combined use of these drugs in patients with impaired myocardial function.

Second, drug interactions may depress electrical activity. Asystole has been reported in two patients on beta-blockers who were given intravenous verapamil.² Both of these patients had normal A/V conduction. Patients with impaired A/V conduction or the sick sinus syndrome should be treated with great caution with combinations of verapamil and beta-blockers.

Serious electrophysiologic side effects have been reported with combinations of disopyramide and beta-blocking drugs. Gelijster and Haeghebaert reported severe bradycardia and no effective cardiac output in a 56-year-old man with myocardial infarction who was being treated with disopyramide and who had previously been given practolol.

Cumming and Robertson reported two cases of supraventricular tachycardia in which severe hypotension and bradycardia occurred when practolol and disopyramide were used together.

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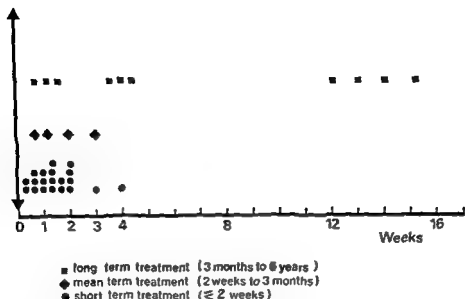


Fig 3 Delay before relapse of chronic arrhythmias after cessation of treatment. In 34 patients in whom the recurrence of the arrhythmia could be evaluated it occurred within 2 weeks in 24, after 3 to 4 weeks in six, and after 12 to 16 weeks in four.

arrhythmias (Fig 5). Its mean value was 3.3 weeks and in 24 cases it was 2 weeks or less. The duration of treatment and child's age affect the delay before relapse. In 10 treatments lasting between 3 months and 6 years, relapses occurred three times in 2 weeks, three times in 4 weeks, and four times in 2 to 3 months.

Concerning children and long term treatments, particular attention must be paid to drug tolerance. Electrocardiographically, repolarization changes must occur before a treatment failure is accepted, i.e. before the appearance of increased height of U waves and lengthening of the Q-T segment. The sinus rate was steadily reduced but in only 10 cases was it less than 60/min at rest and in seven of these patients there was a preexisting atrial rhythm disturbance. The three cases of sinoatrial block were preexisting. We observed no intra-atrial conduction disturbances. The P-R lengthening was from 40 to 80 msec in 41 cases with Wenckebach periods in three cases. We observed no distal A-V conduction disturbance in spite of 52 cases of complete right bundle branch block, 15 of which were associated with a left anterior hemiblock. The QRS duration increased by 20 to 40 msec in two cases of incomplete right bundle branch block.

Corneal deposition (three cases), photosensitivity (four cases), and bluish skin coloring (one case after 72 months of treatment) were rarely observed and only in older children. In four cases

Table III Amiodarone efficacy according to localization of arrhythmias

| Results | Atrial | | Junctional | | Ventricular | |
|---------------------|----------|-----|------------|-----|-------------|-----|
| | 93 cases | 69% | 22 cases | 16% | 20 cases | 15% |
| Good (81 cases 80%) | 55 cases | 41% | 12 cases | 9% | 14 cases | 10% |
| Fair (44 cases 33%) | 31 cases | 23% | 10 cases | 7% | 3 cases | 2% |
| Poor (10 cases 7%) | 7 cases | 5% | 0 cases | | 3 cases | 2% |

Table IV Amiodarone efficacy according to resistance to prior treatment

| Results | Prior treatments ineffective | | Amiodarone as first treatment | |
|---------------------|------------------------------|-----|-------------------------------|-----|
| | 4 cases | 5% | 61 cases | 45% |
| Good (81 cases 60%) | 41 cases | 30% | 40 cases | 30% |
| Fair (44 cases 33%) | 30 cases | 23% | 14 cases | 10% |
| Poor (10 cases 7%) | 3 cases | 2% | 7 cases | 5% |

nightmares, hallucinations, and personality problems caused the cessation of treatment. These signs seemed to be precursors of hyperthyroidism; in two other cases they appeared before obvious biologic modifications. Conversely, one patient developed hypothyroidism, which may have reflected a predisposition (control cholesterol

Table 1 Hemodynamic results (mean \pm 1 SD)

| Data | Control | Immed after metoprolol | 15 min after metoprolol | Immed after tocainide | 15 min after tocainide |
|---|-----------------|------------------------------|-------------------------------|-----------------------------|------------------------------|
| Heart rate/min | 79 \pm 13 | 68 \pm 10 | 66 \pm 15 | 68 \pm 14 | 67 \pm 10 |
| | $P < 0.01$ | | | | |
| | $P < 0.01$ | | | | |
| Cardiac index (L/min/m ²) | 3.49 \pm 1.53 | 2.97 \pm 1.77 | 2.80 \pm 1.64 | 2.2 \pm 1.28 | 2.21 \pm 1.3 |
| | $P < 0.05$ | | | | |
| | $P < 0.01$ | | | | |
| LV max dP/dt (mm Hg/sec) | 1510 \pm 370 | 1378 \pm 313 | 1246 \pm 304 | 997 \pm 277 | 1007 \pm 338 |
| | $P < 0.05$ | | | $P < 0.01$ | |
| | $P < 0.01$ | | | $P < 0.001$ | |
| LV stroke work index (gm/beat/m ²) | 64.9 \pm 33.2 | 59.2 \pm 31.9 | 58.1 \pm 31.5 | 44.6 \pm 20.2 | 42.9 \pm 26.9 |
| | $P < 0.05$ | | | $P < 0.05$ | |
| | $P < 0.01$ | | | $P < 0.05$ | |
| LV end-diastolic pressure (mm Hg) | 24 \pm 9 | 20 \pm 10 | 20 \pm 9 | 24 \pm 8 | 26 \pm 7 |
| Mean pulmonary artery pressure (mm Hg) | 16 \pm 8 | 17 \pm 8 | 18 \pm 8 | 22 \pm 8 | 23 \pm 8 |
| Mean pulmonary artery pressure (mm Hg) | 23 \pm 10 | 23 \pm 9 | 23 \pm 10 | 27 \pm 10 | 27 \pm 10 |
| | $P < 0.05$ | | | | |
| End diastolic dimension (cm) | 6.2 \pm 1.4 | 6.1 \pm 1.3 | 6.1 \pm 1.0 | 6.4 \pm 1.1 | 6.0 \pm 1.0 |
| Echo ejection fraction (%) | 67 \pm 16 | 60 \pm 12 | 53 \pm 10 | 52 \pm 10 | 44 \pm 13 |
| | $P < 0.01$ | | | $P < 0.01$ | |
| Mean V ₁ (circ/sec) | 0.78 \pm 0.19 | 0.73 \pm 0.16 | 0.64 \pm 0.17 | 0.5 \pm 0.06 | 0.48 \pm 0.04 |
| | $P < 0.01$ | | | $P < 0.05$ | |

One of these patients died. The other developed a further episode of supraventricular tachycardia which was treated without untoward effect by disopyramide alone. This suggests that it is the combination rather than the individual drug that leads to problems. The combined use of beta blockers and disopyramide is relatively contraindicated.

Amiodarone, a new antiarrhythmic drug, has also been reported to cause asystole and severe bradycardia when given in close proximity to propranolol. Asystole and depression of myocardial contractility have also been reported with propranolol therapy for digitalis toxicity. This complication is frequent enough to preclude beta blocker treatment for digitalis toxicity unless everything else has failed.

A third type of interaction is where one drug interferes with the pharmacokinetics of another. Administration of propranolol reduces the clearance of lidocaine and quinidine.

We studied the hemodynamic electrophysio-

logic and pharmacokinetic effects of tocainide in patients who were given intravenous metoprolol shortly before tocainide.

Material and methods

Hemodynamic interactions of tocainide. Hemodynamic observations were made on six patients, five men and one woman, undergoing routine diagnostic catheter studies. A Swan-Ganz catheter was positioned in the pulmonary artery for measurement of pressure and thermal dilution cardiac output. The left ventricular pressure was measured by means of a Millar catheter tip manometer. Left ventricular dimensions were recorded simultaneously by M-mode echocardiography. Following control measurements, metoprolol was infused in a dose of 0.20 mg/kg over a 5 minute period. Hemodynamic and echo measurements were recorded at the end of the infusion and 15 minutes later. Tocainide was then infused in a dose of 0.70 mg/kg/min over a 15 minute period. Hemodynamic measurements

260 gm/L) In these three patients the thyroid dysfunction (two hyperthyroid one hypothyroid) completely regressed in several weeks with cessation of treatment Biologic surveillance confirms the rarity of thyroid complications in the present experience plasma cholesterol levels Hamolsky test T_3 , T_4 and TSH were monitored before and after a mean duration of 14.5 months of treatment in 40 patients No variation exceeding the normal range for these tests was observed except in the three previously mentioned patients

Discussion

After amiodarone has been used for more than 10 years as an antiarrhythmic in adults, it is not necessary to emphasize its effectiveness and uniqueness However its overall effectiveness does not replace other antiarrhythmics and moreover its problems of tolerance or thyroid toxicity should not make it an initial simple therapeutic approach These side effects were carefully considered before this drug was used in children and only its extraordinary effectiveness and the observed excellent tolerance encouraged us to increase its use over the 9 year period We know of only one equivalent experience (Kreutzer BA Personal communication)

Amiodarone cured or improved arrhythmias in six out of ten patients and improved their tolerance in three out of four remaining patients whatever the mechanism localization and previous resistance This is without evidence of poor tolerance or nonreversible toxicity and represents almost all the desirable properties for an ideal antiarrhythmic It is mostly on a matter of principle that one should not use this as the first medication in children's rhythm disturbances even though it is more consistently effective and better tolerated than in adults

The drug is metabolized more rapidly in children with the onset of action in 4 days instead of 10 days as in adults and effectiveness after cessation lasts less than a few weeks as opposed to several months in adults These are the norms found in animal experiments from which we also know that the drug concentration in the adipose tissue and muscle is 10 to 30 times greater than in the plasma There is no plasma assay to regulate the dosage used in a clinical setting and in any case the tissue binding might invalidate normal pharmacokinetic parameters and should not be interpreted as rigorously as for other drugs The

fact that children have less adipose tissue than adults may account for the faster metabolism in the former but probably this is not the only difference and does not explain the unique phenomenon of corneal deposits in adults The drug's primary and secondary effects obviously vary with age and this is clearly visible in the older child who tends to react as an adult

It is in this regard that the younger the child and the more recent the arrhythmia the more oral amiodarone is likely to be an effective emergency treatment able in a few hours to terminate a reciprocal junctional paroxysmal tachycardia or an atrial or ventricular tachycardia while avoiding the dangers of other antiarrhythmics The mechanism of action of amiodarone is clearly known and it reduces the outward potassium current as well as the rapid inward sodium current without being classed as a membrane stabilizing agent Also it is not a beta blocker but nevertheless slows the beta response Finally it has no effect on the slow calcium canal and its essential action is to lengthen the duration of the action potential and refractory period A single mechanism of action seems to fit poorly with the drug's widespread effectiveness in a great many different arrhythmias It is rare to combine amiodarone with other antiarrhythmics with the exception of digitalis whose supraventricular antiarrhythmic action is synergic In addition digitalis alone can compensate for amiodarone's real although moderate depressive myocardial effect

The demonstration of wide clinical efficacy does not dictate indications for medication However one can recognize cases in which one should directly resort to this treatment In practice this applies to all poorly tolerated arrhythmias, as it is the least dangerous in the presence of poor myocardium In the long run it does not necessarily have to be maintained except in special resistant life or death childhood arrhythmias as such certain long term atrial tachycardias, chronic reciprocal tachycardias, ectopic focus tachycardias in infants and catecholergic ventricular tachycardias when not controlled by beta blocking treatment

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Table II Electrophysiologic results (mean \pm 1 SD)

| Data | Control | Immed after metoprolol | Immed after tocainide | After tocainide |
|--|--|--|--|--|
| Heart rate/min | 66 \pm 8 | 71 \pm 13 | 73 \pm 1 ^a | 74 \pm 10 |
| A-H interval (msec) | 73 \pm 10 | 81 \pm 8 | 89 \pm 12 | 81 \pm 13 |
| | $P < 0.02$ | | | |
| H-V interval (msec) | 37 \pm 7 | 40 \pm 6 | 44 \pm 7 | 39 \pm 5 |
| Corrected sinus node recovery time at atrial pacing rate of 100/min (msec) | 293 \pm 222 | 278 \pm 212 | 291 \pm 125 | 375 \pm 149 |
| Corrected sinus node recovery time pacing rate $>$ 100/min (msec) | 157 \pm 130 | 195 \pm 65 | 336 \pm 160 | 298 \pm 119 |
| | | | $P < 0.05$ | |
| Atrial pacing rate at onset of A-V Wenckebach block (beats/min) | 169 \pm 16 | 148 \pm 25 | 147 \pm 27 | 145 \pm 28 |
| | $P < 0.02$ | | | |
| Left effective refractory period (msec) | 278 \pm 63 | 239 \pm 45 | 246 \pm 38 | 247 \pm 1 |
| Left functional refractory period (msec) | 294 \pm 62 | 267 \pm 54 | 277 \pm 51 | 28 \pm 51 |
| AV nodal effective refractory period (msec) | 320 \pm 47 | 313 \pm 66 | 321 \pm 75 | 300 \pm 34 |
| AV nodal functional refractory period (msec) | 390 \pm 44 | 399 \pm 73 | 399 \pm 94 | 405 \pm 26 |
| His-Purkinje effective refractory period (msec) | 395 \pm 44 | 418 \pm 40 | 430 \pm 52 | 400 \pm 36 |
| His-Purkinje functional refractory period (msec) | 401 \pm 36 | 421 \pm 40 | 431 \pm 54 | 400 \pm 35 |
| | | | $P < 0.05$ | |
| | | | $P < 0.01$ | |
| Right ventricular effective refrac- tory | 236 \pm 60 | 249 \pm 34 | 217 \pm 26 | 211 \pm 26 |
| Presence of ventriculoatrial (VA) conduction at right ventricular pacing rate of 100/min | 4/8 = 1:1 VA conduction 4/8 = 0 VA conduction | 3/8 = 1:1 VA conduction 1 = Wenckebach | 3/8 = 1:1 VA conduction 1 = Wenckebach | 3 = 1:1 VA conduction 1 = 2:1 VA block |

were repeated at the end of the infusion and 15 minutes later. Plasma levels of both drugs were measured at the time of hemodynamic measurements.

Electrophysiologic interactions of tocainide

The electrophysiologic effects of metoprolol and tocainide were assessed in eight patients (five males and three females) who were undergoing diagnostic studies for investigations of palpitations or dizziness. They were premedicated with hypnotic doses of pentobarbitone. All antiarrhythmic medication has been withdrawn 48 hours previously. Bipolar catheters were inserted via the femoral veins into the right ventricle and also in a position to record the His bundle electrogram. A quadripolar catheter was introduced via

the right arm into the right atrium. Another bipolar catheter was placed in the coronary sinus. The intracardiac signals from these catheters were recorded together with the Frank XYZ leads. Measurements of basic intracardiac conduction intervals, sinus node recovery time, corrected sinus node recovery time, and refractory periods of the atrium, A-V node, and right ventricle were determined by programmed stimulation. Paper speed was 200 mm/sec for all studies and basic His electrogram interpretation standards were applied.

Following control measurements the same basic doses and protocol design as in the hemodynamic study were used except that since the various electrical tests took longer they could be

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Table III Plasma levels of metoprolol and tocainide (mean \pm 1 SD)

| Metoprolol and tocainide | Haemodynamic study | | | |
|---------------------------|--------------------------------|-------------------------------|-------------------------------|-------------------------------|
| | Immed after metoprolol | 15 min after metoprolol | Immed after tocainide | 15 min after tocainide |
| Metoprolol (μ mol/L) | 0.49 \pm 0.12 | 0.17 \pm 0.05 | 0.70 \pm 0.07 | 0.17 \pm 0.06 |
| Tocainide (μ mol/L) | 0 | 0 | 83.0 \pm 49.5 | 41.6 \pm 3.9 |
| Metoprolol and tocainide | Electrophysiologic study | | | |
| | 15 min after end of metoprolol | 15 min after end of tocainide | 30 min after end of tocainide | 45 min after end of tocainide |
| Metoprolol (μ mol/L) | 0.77 \pm 0.13 | 0.14 \pm 0.05 | 0.13 \pm 0.03 | 0.11 \pm 0.04 |
| Tocainide (μ mol/L) | 0 | 32.3 \pm 6.6 | 11.7 \pm 5.5 | 2.4 \pm 4.9 |

Therapeutic ranges: (1) Tocainide 80-160 μ mol/L and (2) metoprolol 0.2 to 0.6 μ mol/L. (3) The therapeutic range levels are proportional to those produced by 100 mg b.i.d. dose.

done once after metoprolol and twice after tocainide

Results

Hemodynamic interactions The hemodynamic findings are summarized in Table I. There was a significant fall in heart rate and cardiac output following metoprolol but no additional fall after tocainide. Left ventricular dP/dt max fell significantly after beta blockade and there was a further fall after tocainide. Left ventricular end diastolic pressure was not altered significantly although pulmonary wedge pressure rose after tocainide but not after metoprolol. Echo end diastolic dimensions were not altered after either drug. There was a significant fall in mean V₁ and ejection fraction 15 minutes after metoprolol and again 15 minutes after tocainide.

Electrophysiologic interactions The electrophysiologic results are detailed in Table II. There was no change in resting heart rate. The A-H interval increased significantly after metoprolol but was not further affected by tocainide. The H-V interval was unchanged. The corrected sinus node recovery time was not significantly altered during the study except that at pacing rates over 100/min there was a significant lengthening following tocainide administration. The atrial pacing rate required to induce A-V Wenckebach effect was significantly decreased by metoprolol but was not further altered by tocainide. The refractory periods both functional and effective of the atrium, A-V node and right ventricle showed no significant change. There was however

a significant shortening of the His-Purkinje system. There was no consistent action on ventriculoatrial conduction (Table II).

Discussion

In our study metoprolol and tocainide singly and in combination appeared to have little influence on electrophysiologic parameters in patients who were free from sinus node disease or impaired A-V conduction. However, when this protocol was administered to patients with underlying electrophysiologic abnormalities there was serious depression of sinus node function and A-V conduction.

The plasma levels of both drugs remained in the therapeutic range (Table III). There was no obvious evidence of pharmacokinetic interaction although this was not a formal pharmacokinetic study. The plasma levels of both drugs immediately after infusion in the hemodynamic study were much higher than those in the electrophysiologic study. This probably reflects a difference in sampling technique in that samples for the hemodynamic studies were taken from the right atrium while those for the electrophysiologic study were taken from a peripheral vein in the left arm.

In conclusion the administration of tocainide and metoprolol to patients with heart disease results in a small depression of myocardial contractility. This does not result in clinical sequelae. Administration of the drugs especially metoprolol results in a mild depression of A-V nodal conduction. Tocainide shortens the functional

The clinical use of intravenous verapamil

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The mechanisms of action and clinical application of verapamil—a calcium ion antagonist—are reviewed. Verapamil is effective and has important application in the treatment of coronary artery spasm, hypertensive crises and supraventricular tachyarrhythmias.

Present day pharmacologic practice usually takes the form of what might well be termed variations on a theme. There are for example many variations on the penicillin theme, numerous permutations on the phenothiazine theme and a thematic multiplicity of beta blocking agents. Only rarely is there an event that truly constitutes a major pharmacologic breakthrough, a breakthrough that reflects the development of an entirely new pharmacologic principle with dramatic clinical effects and exciting potential. The introduction of calcium ion antagonists heralded by verapamil constituted such an event. An event moreover that was no novel in pharmacologic action that it necessitated the addition of a fourth class to the original three class classification of antiarrhythmic substances by Singh and Vaughan Williams. This new class of drugs not only inhibits the transmembrane transport of calcium ions but affects the relationship between excitation-contraction coupling with profound effects on smooth muscle, particularly vascular smooth muscle and on myocardial inotropism effects which have important application to clinical and especially cardiologic therapy.

Basic pharmacologic action

Verapamil has three basic pharmacologic effects: (1) it restricts the conversion of ATP to ADP; (2) it delays or blocks conduction within the A-V node; and (3) it diminishes vascular and other smooth muscle tone.

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Restriction in the conversion of ATP to ADP
Verapamil blocks or restricts the conversion of ATP to ADP and the consequent release of a high energy phosphate bond. This results in a reduction of high energy phosphate consumption which in turn leads to a reduction in contractile tension. The oxygen requirements of cardiac muscle are thereby decreased.

Delay or block of conduction within the A-V node
A-V nodal delay or block has two major therapeutic implications: (1) Supraventricular impulses of atrial tachycardia, atrial flutter or atrial fibrillation will be subject to increasing A-V block. This will reduce the ventricular response with a consequent reduction of ventricular rate. (2) The circus movement of a reciprocating supraventricular tachycardia will be interrupted within the A-V node and the tachycardia thereby terminated.

Diminution of vascular tone
Diminution of vascular tone results in: (1) coronary dilatation which thereby improves myocardial oxygen supply and (2) peripheral vasodilatation which results in a reduction in peripheral resistance with a consequent reduction in blood pressure. Furthermore, the reduction in peripheral resistance will also reduce the cardiac afterload and thereby the workload of the heart.

Electrophysiologic effect

The plateau phase—phase 2—of the cardiac action potential is due at least in part, to a slow inward flow of calcium ions into the cell. Verapamil blocks or retards this slow inward flow of calcium ions and thereby slows or prolongs both phases 2 and 3 of the cardiac action potential. It has no effect on the other phases, thereby indicating

refractory period of the His Purkinje system. Apart from this there is little effect on conventional electrophysiologic indices in patients who are free from sinus atrial or A V nodal disease. Thus they can be used with reasonable safety in these patients. However, in patients with the sick sinus syndrome and impaired A V conduction significant depression of function occurs. Hence their combined use in these situations is to be avoided.

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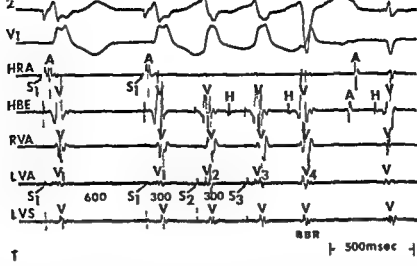


Fig 4 Bundle branch reentry following left ventricular stimulation. From top to bottom are ECG Leads 2 and V₁ and electrograms from the high right atrium (HRA) His bundle region (HBE) right ventricular apex (RVA) left ventricular apex (LVA) and left ventricular septum (LVS). Two ventricular extrastimuli (S₁, S₂) are each delivered at a coupling interval of 300 msec after the eighth complex of simultaneous right atrial and left ventricular pacing (S₁, S₂) at a cycle length of 600 msec. S₁ is followed by a repetitive ventricular response (V₁) due to achievement of marked retrograde His Purkinje conduction delay (V₁H₁) prolongation. The H₁V₁ interval of the extra complex (V₁) is 45 msec and is identical to that of the sinus complex. V₁ is similar in morphology to the paced complexes. BBR = bundle branch reentry.

usually had a configuration similar to the paced complex and was preceded by a His potential with an H₁V₁ interval equal to or greater than that of a normally conducted antegrade impulse. Intraventricular reentry was defined by reproducible initiation of extra ventricular complexes which were independent of V₁H₁ prolongation and which occurred in the absence of His potentials or with His potentials with an H₁V₁ interval less than that observed during sinus rhythm.

The occurrence of sustained ventricular tachycardia was not considered diagnostic of intraventricular reentry unless patients also demonstrated in addition isolated repetitive responses.

Data from the first 250 patients in this series were reviewed retrospectively and the next 150 patients were studied prospectively. Results were comparable and thus were analyzed as a historical cohort. Statistical significance was determined by chi square analysis.

Results

Incidence of repetitive ventricular responses—relationship to organic heart disease. Two hundred and thirty eight of the 400 patients (59.5%) manifested some form of repetitive ventricular response. One hundred sixty (40%) had

Table I

| | OHD (289 pts.) | NHD (111 pts.) |
|------|----------------|----------------|
| BBR | 153 (108) | 60 (5%) |
| IVR | 69 (24) | 9 (1) |
| Both | 45 | 8 |

BBR = bundle branch reentry. IVR = intraventricular reentry. OHD = organic heart disease. NHD = No heart disease.

Number in parentheses are the number of patients with isolated BBR and IVR.

isolated bundle branch reentry 25 (6.3%) had isolated intraventricular reentry and 53 (13.3%) had both bundle branch reentry and intraventricular reentry (Fig 3 Table I). Repetitive ventricular responses were observed in 177 of 289 (61.2%) patients with organic heart disease and in 61 of 111 patients (55%) without organic heart disease ($p > 0.10$).

Intraventricular reentry. Sixty nine of 289 (23.9%) patients with organic heart disease and nine of 111 (8.1%) patients without heart disease had intraventricular reentry ($p < 0.005$). Conversely of the 78 patients with intraventricular reentry 69 (88.5%) had organic heart disease while nine of 78 (11.5%) were free of demonstrable heart disease ($p < 0.001$). Of 58 patients with

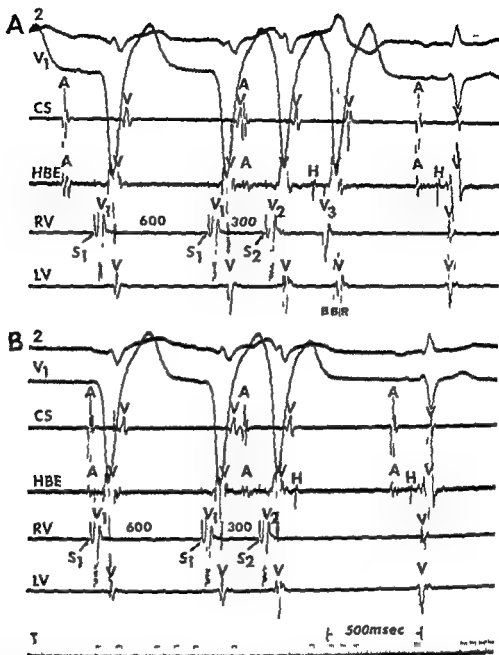


Fig 5 Abolition of bundle branch reentry by preexcitation of the His bundle. The panels are organized from top to bottom as ECG Leads 2 and V₁ and coronary sinus (CS) His bundle (HBE) right ventricular (RV) and left ventricular (LV) electrograms. In panel A a premature RV stimulus (S₁) at a coupling interval of 300 msec results in bundle branch reentry (BBR). In panel B S₁ is again delivered at a coupling interval of 300 msec but no BBR occurs. BBR is prevented by a spontaneous sinus complex preceding V₁ which conducts through the A-V node to pre-excite the His bundle by 40 msec thereby rendering it refractory to retrograde activation. The supraventricular impulse blocks below the His bundle and no ventricular response occurs.

documented ventricular tachycardia or ventricular fibrillation 43 (74%) also had repetitive ventricular responses due to intraventricular reentry following ventricular stimulation. The intraventricular reentrant complexes in these patients were morphologically similar to their spontaneous or subsequently induced tachyarrhythmias

(Fig 2). Twenty five (58%) of these 43 patients manifested isolated intraventricular reentry while the remaining 18 demonstrated both intraventricular reentry and bundle branch reentry. However intraventricular reentry occurred in only 9.1% (31 of 342) of patients without malignant ventricular arrhythmias ($p < 0.001$). None

Shortcomings of the Lown grading system for observational or experimental studies in ischemic heart disease

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The Lown grading system uses three levels of frequency and four complex features to grade ventricular arrhythmias. The seven Lown grades are mutually exclusive (a patient can be in only one grade) and hierarchical (higher grades indicate increased likelihood of death). We evaluated the ability of the Lown arrhythmia grading system to predict death in 400 patients who were convalescing from acute myocardial infarction. Lown grading produced a poor distribution among grades of the population, lacked a monotonic increase in risk with increasing arrhythmia grade, lacked a substantial risk gradient between grades, and showed a lack of isometry in the higher grades. Also, the Lown grading system thwarts the use of standard multivariate techniques for relating the frequency and characteristics of ventricular premature depolarizations (VPDs) to cardiac death. We also examined the utility of the Lown arrhythmia equation for evaluating the results of antiarrhythmic drug therapy. The Lown grading system failed to reveal clearly the change in VPD frequency and characteristics as a function of drug dose. We propose an alternative grading system that is not mutually exclusive or hierarchical. This grading system lacks many of the flaws of the Lown grading system and is suitable for standard multivariate analyses but like the Lown grading system still fails to show the relationships among ventricular arrhythmias, time drug dose, and activity.

In 1971 Lown and Wolf¹ proposed a grading system for ventricular arrhythmias. They contended that ventricular arrhythmias are so common in ischemic heart disease that their mere presence has little significance. However, these authors argued further that certain characteristics of ventricular premature depolarization (VPD) do identify persons who are prone to sudden cardiac death: these characteristics are high frequency, multiform VPDs, repetitive VPDs, and early cycle VPDs. Using these VPD features, they devised a system to grade ventricular arrhythmias in terms of prognostic significance. The VPD grades were arranged in ascending order of gravity, i.e., likelihood of dying. In 1975 the Lown arrhythmia "equation" was introduced primarily for use in experimental studies. In this article we will discuss the shortcomings of

the Lown system for grading ventricular arrhythmias in observational studies and in experimental studies with antiarrhythmic drugs.

Use of Lown grading system in observational studies

The Lown grading system has been used to study the associations between ventricular arrhythmias and other variables or outcomes, e.g., sudden cardiac death. For example, the Lown grading system has been used to investigate the relationship between ventricular arrhythmias and coronary anatomy or left ventricular dysfunction. In this section we will evaluate the utility of the Lown grading system for predicting outcome in patients who survive acute myocardial infarction. For this purpose we will use a group of 400 patients that we studied during their admission for acute myocardial infarction. Each patient had a 24-hour ECG recording made 10 to 24 days after infarction. These 24-hour ECG tapes were analyzed for ventricular arrhythmias by the digital computer program Columbia IV.

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The automatic implantable defibrillator

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The automatic implantable defibrillator is an electronic device programmed to monitor the cardiac rhythm continuously to recognize ventricular fibrillation and ventricular tachyarrhythmias as characterized by sinusoidal waveform and to deliver corrective defibrillatory discharges when indicated. Three patients suffering from recurrent malignant ventricular arrhythmias refractory to medical therapy underwent permanent implantation of this device. Seven episodes of ventricular tachycardia and flutter/fibrillation were documented during the weeks following the implantations: two were induced at electrophysiologic studies and five occurred spontaneously. All were correctly identified and six were automatically reverted to normal sinus rhythm by the implanted device; one induced episode was cardioverted externally before the unit could recycle. Although many problems remain to be solved and the ultimate value of this therapeutic modality has to be determined, a new approach to prevention of sudden death in patients at high risk of developing lethal ventricular arrhythmias has become available.

The continuing inability to deal effectively with malignant ventricular arrhythmias outside the hospital setting has prompted the development of a clinically applicable automatic implantable defibrillator¹. This device is programmed to monitor the cardiac rhythm continuously to recognize ventricular fibrillation and ventricular tachyarrhythmias characterized by 'sinusoidal waveforms'² and to deliver corrective defibrillatory discharges when indicated. The chief objective of the automatic defibrillator is to protect patients at particularly high risk of sudden death whenever and wherever they are stricken by these lethal arrhythmias.³ In comparison to services provided by a coronary care unit, the implanted device has the unique advantage of being permanently available to the patient at risk without interaction of specialized personnel or the need for additional equipment. Conceptually, the implantable defibrillator is analogous to an implantable demand pacemaker except that mal-

ignant ventricular arrhythmias instead of asystole are sensed and the delivered pulse has appropriate defibrillating characteristics.

Description of the device

The first clinical model of the automatic implantable defibrillator (Fig 1) is encased in titanium and hermetically sealed with a laser weld; it weighs 250 gm and occupies a volume of 145 cc. All materials in contact with body tissue are biocompatible. The defibrillating electrodes are made from titanium and silicone rubber. One electrode designed for placement in the superior vena cava near the right atrial junction is located on the distal end of an intravascular catheter. The second electrode in the form of either a cup or a flexible rectangular patch is placed extracardially over the apex of the heart. The outside surface of the apical electrode is insulated to achieve optimal current distribution.

The device is powered by lithium batteries having a projected monitoring life of approximately 3 years or a discharge capability of approximately 100 shocks. The sensing system detects ventricular fibrillation by monitoring a sampled probability density function of the ven-

Developed and manufactured under the name of AID of Sibley Inc by Medrad, Inc/Intec Systems, Inc Pittsburgh, Pa

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VPD CHARACTERISTICS DETECTED BY LOWN CLASSIFICATION

| | Lown Grade | | | | | |
|-------------------------|------------|---|---|----|----|---|
| | 1 | 2 | 3 | 4A | 4B | 5 |
| VPD < 30/hr | | | | | | |
| VPD ≥ 30/hr | | | | | | |
| MULTIFORM VPD | | | | | | |
| VPD PAIRS | | | | | | |
| VENTRICULAR TACHYCARDIA | | | | | | |
| R-on-T VPD | | | | | | |

Fig 1 The manner in which the Lown grading hierarchy obscures VPD characteristics. The Lown grades are plotted as columns of the matrix and VPD characteristics as rows. The crosshatched cells indicate characteristics that are unknown in each Lown grade. For example, when a patient is in grade 2, all four complex features must be absent. However, in grade 5, there is uncertainty about VPD frequency and the presence of any complex feature except R on T.

Major characteristics of the Lown grading system. The Lown grading system uses three levels of frequency and four complex features to grade ventricular arrhythmias (Table I). The grades are mutually exclusive and hierarchical. The system is mutually exclusive in the sense that a person can only be in one grade. The system is hierarchical in two senses: (1) the grade depends on the rank of the VPD features and (2) higher grades imply higher risk. Each grade is assumed to have a poorer prognosis than those lower in the hierarchy.

Frequency. Since 1971, 0 and 30 VPDs/hour have been used to partition patients into grade I, 1 or 2. It seems reasonable to select 0 VPD/hour as one of the stratifying criteria. However, the rationale for 30 VPDs/hour is less clear. In our 400 postinfarction patients, 10 VPD/hour is at the fiftieth percentile and 10 VPDs/hour is at the seventy-fifth percentile. The Lown criterion for high frequency is at the eighty-seventh percentile, i.e., only 13% of our 400 patients had 30 or more VPDs/hour. Table II compares the frequency criteria of $\geq 1/\text{hour}$, $\geq 10/\text{hour}$ and $\geq 30/\text{hour}$

Table I The Lown grading system

| Lown grade | Definition |
|------------|-------------------------|
| 0 | No VPDs |
| 1 | Less than 30 VPDs/hr |
| 2 | 30 or more VPDs/hr |
| 3 | Multiform VPDs |
| 4A | Paired VPDs |
| 4B | Ventricular tachycardia |
| 5 | R on T VPDs |

Table II Comparison of three VPD frequency criteria for risk stratification in 400 patients after acute myocardial infarction

| Data | VPD frequency | | |
|-------------------------|--------------------|---------------------|---------------------|
| | $\geq 1/\text{hr}$ | $\geq 10/\text{hr}$ | $\geq 30/\text{hr}$ |
| No. of patients | 190 | 99 | 56 |
| No. of deaths | 57 | 37 | 94 |
| Chi square | 23.1 | 23.4 | 1.5 |
| Odds ratio | 3 | 3.6 | 3.6 |
| Sensitivity (%) | 73 | 47 | 30 |
| Specificity (%) | 59 | 81 | 89 |
| False positive rate (%) | 71 | 64 | 11 |
| False negative rate (%) | 10 | 14 | 16 |

for death, sensitivity, specificity, etc. When choosing the partition value for VPD frequency, the physician must consider the action to be taken in the high or low risk stratum. If the low risk group is to receive treatment and follow-up at a reduced level of intensity, the criterion of 1/hour is best. Conversely, if the high risk group is to receive treatment that produces very significant undesirable effects, 30/hour is the best criterion because only about 15% of the population would be exposed to the adverse effects of treatment. For many treatments, the 10/hour criterion may be the best compromise between sensitivity and specificity. It selects the 25% with the highest mortality rate for treatment and thus fails to expose the other 75% to the risks of treatment.

It is important to remember that in the Lown grading system, patients who have complex features are not classified according to VPD frequency. For example, only 85 (30%) of the 280 patients who had a VPD frequency greater than 0/hour but less than 30/hour remained in grade 1. Similarly, only 2 (4%) of the 56 patients with 30 or

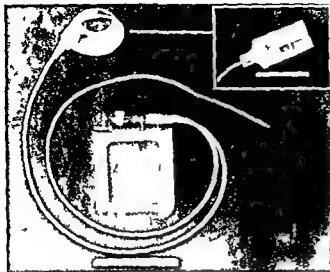


Fig 1 Automatic implantable defibrillator with its two fibrillating electrodes. The insert in the upper right corner shows a patch electrode used as an alternative to the apical cup electrode

tricular electrical activity. This function defines the fraction of time spent by the differentiated input electrogram between two amplitude limits located near zero potential. For all practical purposes ventricular fibrillation is identified by the striking absence of isoelectric segments. The device will also respond to ventricular flutter or ventricular tachycardia characterized by sinusoidal waveform if the probability density function criteria are satisfied. Borderline rate and waveform characteristics of some arrhythmias may result in a delay in detection and thus in the pulse delivery. The important advantages of this method of detection are its reliability, low stand-by power requirements and most important a passive mode of failure. Such a failure mode tends to ensure that possible sensing or mechanical faults will not be interpreted by the device as fibrillation and thus will not result in spurious shocks.

When a suitable ventricular arrhythmia is detected the device delivers a truncated exponential pulse of 25 J 15 to 20 seconds after onset of the arrhythmia. The pulse duration ranges between 3 and 8 msec as a function of the interelectrode resistance. The device can recycle three times if previous discharges are ineffective, with the strength of the third and fourth pulses increased to 30 J. After the fourth discharge about 35 seconds of nonfibrillating rhythm is required to reset the counter and to allow a full

series of pulses to be delivered again at the next episode.

Ancillary equipment

The operational readiness of the automatic defibrillator can be tested prior to and periodically following implantation¹ by an external analyzer*. This noninvasive method involves triggering the capacitor charging cycle of the defibrillator with a magnet briefly placed over the skin in the area of the implanted device. After becoming fully charged the capacitors are automatically discharged into a built-in test load resistor rather than through the leads to the patient. The analyzer measures the charging time by means of an electromagnetic transducer. Progressive increase in this time, normally 10 seconds or less, reflects battery depletion, whereas failure to initiate the cycle indicates an abnormal condition resulting in self deactivation of the device. Continuous application of the magnet over the pulse generator can be used to disable the device completely and to deplete the batteries if needed.

To provide information on the long term performance of the implanted defibrillator, an external recorder† is available for use in selected cases. This small solid state device is triggered by the defibrillator pulse and stores 90 seconds of ECG recording, 22.5 seconds preceding and 67.5 seconds following the discharge. A readout console retrieves this information and indicates the number of arrhythmic episodes, the total number of pulses applied when the episode occurred and the time which elapsed since the last readout.

Preclinical testing

The AID defibrillator has undergone an extensive preclinical testing program to establish its effectiveness, reliability and safety. In addition to acute and chronic animal electrophysiology and pathologic studies, an experimental model was designed in which the clinical syndrome of sudden death from ventricular fibrillation was reproduced in active conscious dogs.¹ In these animals ventricular fibrillation was induced at will by magnetically triggering an implanted alternating current generator connected to the dog's heart through a right ventricular catheter.

* Developed and manufactured under the auspices of AIDCHECK by Medrad Inc./Intec Systems Inc., Pittsburgh, Pa.
† Developed by The Johns Hopkins University Applied Physics Laboratory.

Table III Contribution of frequency to mortality rate in patients in Lown grade 4 or 5

| Lown grade | Average VPD frequency | | |
|------------|-----------------------|-------------|--------------|
| | ≥ 10/hr | < 10/hr | Total |
| Grade 4A | 5/18 (28%) | 3/26 (12%) | 8/44 (18%) |
| Grade 4B | 7/13 (54%) | 0/8 (0%) | 7/21 (33%) |
| Grade 5 | 5/53 (44%) | 9/63 (14%) | 14/116 (9%) |
| Total | 37/84 (44%) | 12/94 (12%) | 49/181 (27%) |

more VPDs per hour remained in grade 2. In either high or low frequency strata the presence of complex features caused considerable movement of patients into higher Lown grades.

Complex features. Complex features are arranged in a hierarchy of assumed increasing risk. Fig 1 lists the Lown VPD grades across the top of the graph and the VPD characteristics on the left. The hatched cells represent VPD characteristics that are unknown in each Lown grade. Note that if any complex VPD characteristic (grade 3 or higher) is present VPD frequency is unknown. The number of unknown VPD characteristics increases as the Lown grade becomes higher so that if a patient has even one R on T VPD all frequency and other complex features are unknown. There are 33 possible combinations of the three frequency levels and four complex features. In our group of 400 patients 28 of the 33 possible combinations were observed. The failure to observe some of the theoretically possible combinations probably results either from low prevalence of some features (eg ventricular tachycardia) and/or interactions among the VPD characteristics. Fig 2 shows the strength of the associations among high frequency VPDs (≥ 30 VPDs/hour) and the four complex features. The strongest associations were between high frequency and pairs or ventricular tachycardia and between pairs and ventricular tachycardia. For example recordings with high VPD frequency are 16.7 times as likely to contain ventricular tachycardia as those with low VPD frequency.

Feinstein recommends that multiple groups be combined only if each group has a similar relationship to the target outcome. We tested the homogeneity among the 16 subgroups in grade 5 with respect to mortality rate. Of the 116 patients in grade 5 23 (20%) had R on T as the only complex feature; the mortality rate in this group was 8.7%. Also in grade 5 21 patients (18%) had

STRENGTH OF ASSOCIATION (ODDS) AMONG VPD CHARACTERISTICS

| | F | M | P | V | R |
|---|---|-----|-------|-------|-----|
| F | | 4.9 | 15.1* | 16.7* | 3.8 |
| M | | | 6.2 | 4.8 | 3.8 |
| P | | | | 19.6* | 4.0 |
| V | | | | | 3.6 |
| R | | | | | |

Fig 2 The associations among VPD characteristics in 400 postinfarction patients. The five characteristics used in the Lown grading system are cross-associated using the odds ratio as a measure of strength of association. F = VPD frequency of 30/hour or greater; M = multiform VPD; P = paired VPD; V = ventricular tachycardia; R = R on T VPD. Since the table is symmetric only the upper half of the matrix is given. Asterisks indicate the strongest associations.

all four complex features; the mortality rate in this group was 62%. Thus subgroups with eight-fold differences in mortality rates are aggregated into Lown grade 5. We conclude that interactions among VPD characteristics significantly alter prognostic significance and that aggregation of different combinations of features into higher Lown grades obscures important information about prognosis.

Lown and his colleagues currently believe that VPD frequency has little prognostic significance in patients with ischemic heart disease; they believe that only grades 4 and 5 predict an adverse outcome. We examined the conditional probabilities of dying given the presence or absence of a VPD frequency of 10/hour or more in Lown grades 4 and 5; these data are summarized in Table III. In grades 4A, 4B, and 5 the proportion of patients dying was significantly greater when VPD frequency was 10/hour or greater. This finding demonstrates that VPD frequency does make an important contribution to the risk of dying in patients who have repetitive or R on T VPDs. In grade 5 the mortality rate when neither pairs nor ventricular tachycardia are present is 10.3%; in contrast the mortality rate is 48.3% when either pairs or ventricular tachycardia are present along with R on T ($P < 0.01$). Thus R on T has little prognostic significance unless associated with repetitive VPDs.

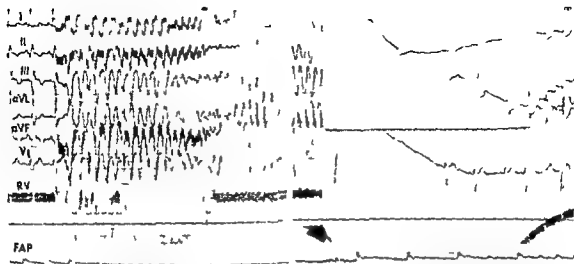


Fig 2 Left panel Initiation of ventricular flutter/fibrillation by a burst of rapid ventricular pacing Right panel arrow Automatic reversion of the arrhythmia to normal sinus rhythm by the implanted defibrillator I II III aVL aVF and V are standard ECG lead RV = right ventricular electrogram FAP = femoral artery pressure

The resulting arrhythmia leads to circulatory arrest and syncope within seconds, thus creating conditions for determining the long term effects and performance of the implanted device.

The preclinical testing also included the analysis of long term bench performance of the implantable defibrillator and of the effects of its exposure to various physical stresses such as vacuum pressure, temperature cycling, mechanical vibration, mechanical shock and electromagnetic interference signals. Despite the fact that many of the test conditions exceeded the standards required of implanted pacemakers, the results were generally satisfactory and the few detected failure modes were analyzed and corrected. The AID defibrillator also underwent an independent evaluation by the Applied Physics Laboratory of The Johns Hopkins University, which included basic device design, provocative challenges to the sensing system and analysis of components, manufacturing and quality control procedures and preclinical test results. On the basis of these data, the device was found suitable for use in a clinical setting.

Preliminary clinical data

A pilot study of the automatic defibrillator is presently being carried out at The Johns Hopkins Hospital in patients suffering from recurrent ventricular tachyarrhythmias refractory to medical therapy. Specifically, the candidates for implantation must have survived at least two episodes of cardiac arrest not associated with acute myocardial infarction with ventricular fibrillation documented electrocardiographically at least once. One such episode must have occurred despite treatment with a medication suppressing all complex ventricular arrhythmias present or failing that despite treatment with two conventional antiarrhythmic agents given simultaneously and resulting in satisfactory blood levels. Patients were excluded if they had other chronic or acute illness, were on drugs other than antiarrhythmics but known to influence electrical activity of the heart or had psychological disabilities. The extremely poor prognosis of patients fulfilling these criteria is exemplified by the fact that four patients identified as potential candidates for implantations of the automatic defibrillator died before they could be transferred to The Johns Hopkins Hospital.

Between February and May 1980 the first three patients underwent implantation of the automatic defibrillator. This group included a 57 year old woman with coronary artery disease, a 16 year old boy with idiopathic cardiomyopathy and a 43 year old man with asymmetric hypertrophic cardiomyopathy. All of these patients suffered from numerous episodes of ventricular fibrillation and hypotensive ventricular tachycardia requiring multiple resuscitations and external defibrillations. On electrophysiologic

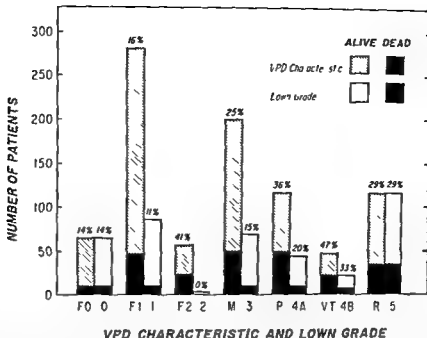


Fig 3 Comparison of VPD characteristics and Lown grades in 400 patients with ischemic heart disease. Each pair of bars compares the Lown grade (right) with the characteristic that makes a person eligible for that grade. FO = VPD frequency = 0; F1 = VPD frequency > 0 < 30; F2 = VPD frequency > 30; M = multifocal VPD; P = paired VPD; VT = ventricular tachycardia; and R = R on T VPD. Deaths in each category are indicated by the black (lower) portion of the bars; the percentages at the top of each bar represent the category specific mortality rates. In grades 1 through 4B there are striking differences between the Lown grade and the characteristic that make a patient eligible for that grade.

These findings serve to illustrate failings of the Lown grading system. In the higher Lown grades frequency and other complex features do contribute to the risk of subsequent death. The presence and intensity of these influences are hidden by the Lown grading system.

Validity of the Lown grading system. Feinstein has discussed criteria for judging the validity of prognostic grading systems. He gives four main criteria: (1) distribution of the population among the categories; (2) monotonicity; (3) total gradient; and (4) isometry of clusters.

Distribution of population. When developing a grading system one hopes for a reasonably symmetric distribution among the categories with more persons in the middle than in the extreme grades. Grade 2 of the Lown system presents a problem in this respect. In ischemic heart disease populations less than 1% will be in grade 2. This represents a technical flaw in the Lown grading system when it is used in ischemic heart disease populations.

Monotonicity. If a grading system is intended to predict mortality rate then the mortality rate should increase monotonically as the grade

increases. If a partition (i.e. grade) has been ranked according to entities that do not necessarily reflect severity a monotonic trend may not occur.¹⁰ Fig 3 gives the mortality rate by Lown grade. There is a notable lack of monotonicity in this grading system.

Total gradient. In addition to monotonicity a substantial gradient (e.g. 10%) between grades is desirable. The Lown grading system also lacks this property. There is no significant difference in the mortality rate among the first four Lown grades and there is no significant difference between the last two grades (Fig 3).

Isometry of clusters. Characteristics that are combined into grades should have similar target rates. As shown above subgroups with markedly different rates (9% to 62%) are combined within grade 3. This lack of isometry will cause misclassifications that can be avoided by other grading methods. In observational studies misclassification will cause confounding and mandate larger sample size and expense to detect existing relationships.

Problems arising from mutually exclusive grades. The mutually exclusive and hierarchical

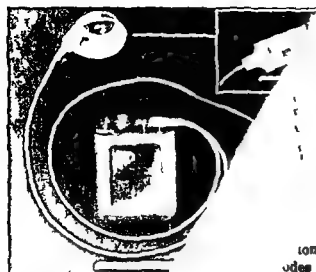


Fig 1 Automatic implant fibrillating electrodes. Th shows a patch electrode cup electrode

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g unsuccessful pulse was
induced ventricular tachycar
ally cardioverted before the
recycled. In another patient a
lar paced rhythm that satisfied the
ensity function criteria triggered the
produced no arrhythmias. Although
igned to treat ventricular fibrilla
device has shown itself to be responsive
ricular tachyarrhythmias other than ven
ar fibrillation that satisfy the probability
ity function criteria" a fact which broadens
ic spectrum of potentially correctable arrhyth
mias

Significantly enough two of our initial three patients were cardioverted on a few occasions by their implanted defibrillator while awake with out feeling undue discomfort or pain. Occasionally the sensation felt was so vague that only a Holter recording confirmed the automatic reversal of the ventricular tachycardia.

These preliminary results are most encouraging and demonstrate that the automatic implantable defibrillator can successfully identify and correct malignant ventricular arrhythmias in man. Although many problems remain to be solved and the ultimate value of this new therapeutic modality has yet to be determined, a new approach has become available for the prevention of sudden death in patients who are at a particularly high risk of developing malignant ventricular arrhythmias.

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Table IV Summary of 24 hour Holter ECG recording

| Time | Data hrs (°) | Heart rate | No of VPDs | No of forms | No of pairs | Epi odes of VT | Occurrences of R on T |
|---------|--------------|------------|------------|-------------|-------------|----------------|-----------------------|
| 10 00 | 88 | 103 | 84 | 3 | 23 | 1 | II |
| 11 00 | 42 | 111 | 1313 | 3 | 93 | 20 | 9 |
| 12 00 | 133 | 114 | 161 | 3 | 131 | 16 | 11 |
| 13 00 | 165 | 116 | 2120 | 3 | 166 | 34 | 16 |
| 14 00 | 252 | 106 | 1047 | 3 | 164 | 40 | II |
| 15 00 | 162 | 104 | 1006 | 3 | 116 | 28 | 10 |
| 16 00 | 245 | 105 | 1377 | 3 | 87 | 40 | 17 |
| 17 00 | 160 | 102 | 1327 | 3 | 8 | 70 | 1 |
| 18 00 | 130 | 109 | 947 | 3 | 91 | 71 | 7 |
| 19 00 | 292 | 111 | 1506 | 3 | 112 | 46 | 12 |
| 20 00 | 158 | 115 | 1067 | 3 | 140 | 49 | 24 |
| 21 00 | 187 | 113 | 2079 | 3 | 704 | 29 | 10 |
| 22 00 | 18 | 83 | 730 | 3 | 43 | 1 | 1 |
| 23 00 | 27 | 91 | 70 | 7 | 44 | 6 | 3 |
| 24 00 | 15 | 90 | 80 | 3 | 70 | 6 | 0 |
| 01 00 | 07 | 90 | 145 | 3 | 7 | 0 | 0 |
| 02 00 | 00 | 88 | 1 | 1 | 1 | 0 | 0 |
| 03 00 | 02 | 84 | 15 | 1 | II | 0 | 0 |
| 04 00 | 05 | 81 | 19 | 3 | 1 | 0 | 0 |
| 05 00 | 07 | 87 | 23 | 3 | 0 | 0 | 0 |
| 06 00 | 10 | 87 | 76 | 3 | 1 | 0 | 1 |
| 07 00 | 07 | 8 | 21 | 3 | 3 | 0 | 1 |
| 08 00 | 00 | 30 | 74 | 0 | 0 | II | II |
| 09 00 | 08 | 92 | 5 | 3 | 0 | 0 | 0 |
| Average | 85 ± 9.2 | 100 ± 12 | 916 ± 89.9 | 3 ± 0.5 | 69 ± 1.2 | 14 ± 1.6 | 6 ± 7 |

grading method used by Lown does not permit investigators to relate the frequency of VPDs to other factors (e.g. left ventricular function) or to relate either frequency or complex VPD features to the mortality rate. Fig 3 shows the prevalence of the three VPD frequency (F) strata ($F = 0$, $0 < F < 30$ and $F \geq 30$) and the four complex features used in Lown grading. These categories are not mutually exclusive. Note the prevalence of frequent and complex VPD features relative to the Lown grade. In Fig 3 it is easy to see that frequent VPD or repetitive VPDs (pairs and ventricular tachycardia) have a very poor prognosis. Also Fig 3 shows how the relationship between VPD frequency or complexity and death is obscured by the Lown grading system.

Alternative grading systems for observational studies. In the previous discussion we have detailed a number of significant problems with the Lown grading system when it is used for observational studies in ischemic heart disease. The system lacks many qualities of an excellent grading system. For observational studies it is better to tabulate VPD frequency and characteristics directly (Table IV). These factors can then

be related to other variables e.g. ischemia or ventricular function or to outcome using univariate or multivariate statistical methods. Such exploration should yield improved prognostic stratification and lead to a better understanding of functional interrelationships in ischemic heart disease.

Use of Lown grading system for experimental studies

A grading system for evaluating antiarrhythmic action should provide an accurate comprehensive concise and understandable summary of ventricular arrhythmias on 24 hour ECG records. In this section we will examine how well the Lown grading system meets these criteria.

Lown arrhythmia equation. To give a more detailed view of arrhythmia response to drug action Lown et al. introduced an equation that describes the arrhythmia grade in each hour of a 24 hour ECG recording. Lown and Graboys¹ suggested that the equation is of special value in assessing antiarrhythmic drug efficacy. The Lown equation lists the Lown arrhythmia grades on a line. For each Lown grade a superscript gives

Clinical use of an implantable automatic tachycardia-terminating pacemaker

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Richard V Calfee Ph D Stanford Calif and Freeport Tex

A significant fraction of patients with supraventricular and ventricular tachycardia remains a therapeutic problem despite improvements in diagnostic testing, new drugs, and improved techniques for the evaluation of the efficacy of drug therapy. Pacing provides an alternative in selected patients. Pacing techniques may be used for arrhythmia suppression or termination and in rare instances may allow the substitution of a more easily managed arrhythmia. We have permanently implanted a new programmable automatic tachycardia terminating pacemaker in patients with drug refractory supraventricular tachycardia. Following pacemaker implantation, successful tachycardia termination has been documented by ambulatory monitoring. Because of changing requirements for effective termination, we feel programmability is mandatory for successful long term efficacy. We conclude that pacemaker therapy of supraventricular tachycardia with the automatic tachycardia terminating pacemaker is safe, effective, and well tolerated.

A significant number of patients with supraventricular tachycardias continues to be a therapeutic problem despite improvements in diagnostic methods, new drugs, and new forms of surgical therapy. A number of techniques for terminating these arrhythmias utilizing pacing stimuli has been described. Two types of implantable pulse generators delivering bursts of rapid atrial stimuli have been available for several years.^{1,2} One is adjustable but must be activated by the patient. The other responds automatically to a tachycardia but is made to prescription and is not adjustable. There is now available a new automatic tachycardia detecting and terminating pacemaker which is multiprogrammable, allowing preimplant and noninvasive postimplant alteration of a wide range of pacemaker functions. We have utilized this system for treating tachycardias in patients referred to Stanford University Medical Center.

Patient selection

Patients were considered for pacemaker therapy if they were drug refractory or their tachycardia

was controlled only at the expense of significant drug side effects. All were adults and all were evaluated by invasive electrophysiologic study. Particular emphasis was placed on the detection of extranodal pathways. Patients with rapidly conducting anterograde pathways were not considered good candidates for pacing therapy because of two potential hazards: (1) The induction of atrial fibrillation resulting in rapid A-V conduction and (2) 1:1 A-V conduction of the terminating burst. In each patient consistently reliable arrhythmia termination had to be demonstrated repeatedly on more than one day.

The tachycardia terminating pacemaker

The pacemaker, the Cyberatch 60 manufactured by Intermedics Inc., is a multiprogrammable bipolar lithium powered device measuring 6 x 4.6 x 1.5 cm and weighing 90 gm. Its functions as a standard inhibited pacemaker with the capacity to automatically respond to tachycardias. The tachycardia terminating response may be inhibited noninvasively. Other programmable variables include two basic pacing rates (60 and 80 beats/min), 15 pulse durations (0.15 to 2.29 msec), and seven input sensitivity levels (0.6 to 2.8 mV). The automatic tachycardia terminating features are also programmable. Twenty-eight combinations of burst rate and duration are available ranging from 180 to 300

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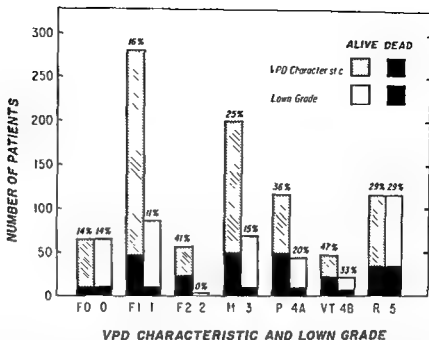


Fig 3 Comparison of VPD characteristics and Lown grades in 400 patients with ischemic heart disease. Each pair of bars compares the Lown grade (right) with the characteristic that makes a person eligible for that grade. FO = VPD frequency = 0; FI = VPD frequency $> 0 < 30$; F2 = VPD frequency > 30 ; M = multifocal VPD; P = paired VPD; VT = ventricular tachycardia; and R = II on T VPD. Deaths in each category are indicated by the black (lower) portion of the bars; the percentages at the top of each bar represent the category-specific mortality rates. In grades 1 through 4B there are striking differences between the Lown grade and the characteristic that make a patient eligible for that grade.

These findings serve to illustrate failings of the Lown grading system. In the higher Lown grades frequency and other complex features do contribute to the risk of subsequent death. The presence and intensity of these influences are hidden by the Lown grading system.

Validity of the Lown grading system. Feinstein¹ has discussed criteria for judging the validity of prognostic grading systems. He gives four main criteria: (1) distribution of the population among the categories; (2) monotonicity; (3) total gradient; and (4) isometry of clusters.

Distribution of population. When developing a grading system one hopes for a reasonably symmetric distribution among the categories with more persons in the middle than in the extreme grades. Grade 2 of the Lown system presents a problem in this respect. In ischemic heart disease populations less than 1% will be in grade 2. This represents a technical flaw in the Lown grading system when it is used in ischemic heart disease populations.

Monotonicity. If a grading system is intended to predict mortality rate then the mortality rate should increase monotonically as the grade

increases. If a partition (i.e., grade) has been ranked according to entities that do not necessarily reflect severity a monotonic trend may not occur.¹⁰ Fig 3 gives the mortality rate by Lown grade. There is a notable lack of monotonicity in this grading system.

Total gradient. In addition to monotonicity a substantial gradient (e.g., 10%) between grades is desirable. The Lown grading system also lacks this property. There is no significant difference in the mortality rate among the first four Lown grades and there is no significant difference between the last two grades (Fig 3).

Isometry of clusters. Characteristics that are combined into grades should have similar target rates. As shown above subgroups with markedly different rates (e.g., 9% to 62%) are combined within grade 5. This lack of isometry will cause misclassifications that can be avoided by other grading methods. In observational studies misclassification will cause confounding and mandate larger sample size and expense to detect existing relationships.

Problems arising from mutually exclusive grades. The mutually exclusive and hierarchical

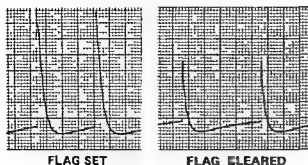


Fig 1 An electronic "flag" is set in the pacemaker circuitry when a tachycardia is sensed producing the telemetry artifact seen in the left trace. After reprogramming this flag is removed (small artifact).

pulses for 1.3 to 5.4 seconds. The presence of an arrhythmia is determined by rate and the criteria are programmable (greater than 137 or 180 beats/min). Input signals with a frequency greater than 300/min are defined as noise. No tachycardia terminating response is delivered and asynchronous pacing is initiated. Application of a magnet converts the device to an asynchronous pacemaker without the tachycardia terminating response.

This pacemaker also has the capacity to collect data regarding the occurrence of tachyarrhythmias to store it and to telemeter it upon command to the evaluating physician. A large amplitude telemetry artifact indicates that the pacemaker has sensed a tachycardia since the last programming (Fig 1). Reprogramming or simply placing a magnet over the pacemaker clears this flag, producing a small amplitude artifact. The pacemaker may be interrogated directly by means of the programmer or by transtelephonic monitoring.

Programmability has been important in maintaining proper pacemaker function in patients implanted with the Cybertach 60. Frequently the burst rate most effective for termination changed after the patient was ambulatory and fully recovered from the effects of hospitalization and previous drug therapy. Maintenance of optimal pacing and sensing levels also necessitated adjustment of pulse duration and sensitivity level. These units have been implanted by means of a transvenous, tined bipolar atrial J electrode. Following interpretation, patients are monitored continuously and the pacemaker response to spontaneous arrhythmia is noted. If adequate

documentation of effective termination is not established by 72 hours, the patient is returned to the electrophysiology laboratory and the arrhythmia is induced (Fig 2). Periodic 24-hour Holter monitoring is carried out in each patient to document efficient termination (Fig 3). Each patient keeps a log of the occurrence of symptoms of tachyarrhythmia. If no symptoms have occurred, the absence of arrhythmia is verified by interrogating the telemetry system of the pacemaker.

The role of automatic pacing termination

Since the initial description by Haft et al,¹ termination of supraventricular tachyarrhythmias by pacing techniques has received steadily increasing interest. A variety of approaches to the management of supraventricular tachycardia by pacing techniques has been described, including single random extrastimuli,² simultaneous A-V sequential pacing,³ dual demand pacing,⁴ orthorhythmic pacing,⁵ and scanning.⁶ In a comparison of a variety of techniques, Fisher et al⁷ demonstrated the greater effectiveness of bursts of rapid atrial stimulation at rates greater than 30 beats/min, faster than the tachyarrhythmia. Patient-activated implantable devices capable of delivering bursts of rapid atrial stimuli are available, and their efficacy in the chronic therapy of supraventricular tachyarrhythmias has been demonstrated.^{8,9,10}

These systems do, however, have several shortcomings: (1) They require that the patient be able to perceive both the presence and absence of tachyarrhythmia. (2) They do not provide for a uniform burst duration since this is controlled by the patient. (3) They require that the patient have constant access to a transmitter in the event that tachycardia should occur. (4) They deliver a large amount of pacing energy to the myocardium (usually greater than 8 volts). (5) They are not effective in patients rapidly disabled by their tachyarrhythmia. (6) They leave a significant residue of symptoms in patients with frequently recurring symptomatic tachycardia due to the time period necessary to perceive the arrhythmia and apply the transmitter.

Custom-built rapid atrial stimulators possess several advantages over radiofrequency devices in that the burst pattern is consistent in terms of energy output and burst duration. In addition, they provide for automatic recognition and anti-

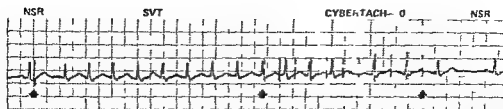


Fig 2 Illustrating the function of the tachycardia terminating pacemaker. On the left hand portion of this continuous ECG strip the rhythm is sinus. A single premature extrastimulus is placed during the relative refractory period of the A-V node, inducing supraventricular tachycardia. After counting eight consecutive intervals shorter than the programmed tachycardia criteria, the pacemaker responds, with a burst of rapid stimuli that terminate the arrhythmia restoring normal sinus rhythm.

BL

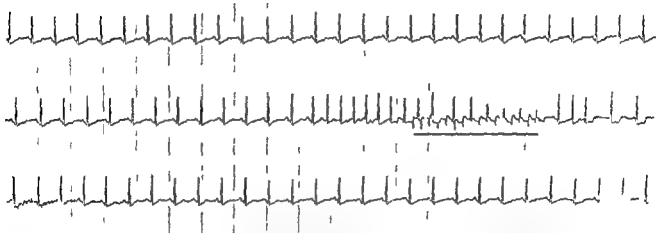


Fig 3 Tracing taken from a 24-hour Holter monitor study illustrates the termination of a spontaneous episode of supraventricular tachycardia. The upper tracing shows 20 seconds of normal sinus rhythm. The middle tracing shows normal sinus rhythm followed by 7 beats of supraventricular tachycardia. The tachycardia terminating pacemaker is then activated for 4 seconds at 240 pulses/min, after which sinus rhythm is restored.

tachycardia response, freeing the patient from the problems of keeping a transmitter available and applying it after the onset of symptoms. However, these units possess significant disadvantages when compared to the programmable automatic burst pacemaker. There is a significant delay once the decision for pacing therapy is made to have a device adjusted and furnished to the implanting physician. Most important, this type of unit does not allow subsequent flexibility to respond to changes in pacemaker requirements. We have found significant changes in the requirements for optimal burst termination between the artificial setting of the catheterization laboratory and the chronic circumstance of an ambulatory patient with a chronically implanted electrode.

The atrial stimulator used in our patients is extensively programmable and fully automatic.

It responds with a burst of stimuli at a uniform rate and duration after sensing eight consecutive RR intervals sufficiently brief in duration to meet the program criteria for the definition of tachycardia. For a tachycardia of 150 beats/min, less than 6 seconds is usually required for sensing and termination. Therefore, patients are usually only transiently aware if at all of the presence and termination of tachycardia.

Due to the extensive programmability, follow-up evaluation of these patients can be quite complete. At each clinic visit, thresholds for pacing and sensing in normal sinus rhythm are determined. In certain patients with easily inducible arrhythmias, pacemaker efficacy can be tested by the application of a magnet. This produces single random extrastimuli which eventually will initiate an episode of tachycardia.

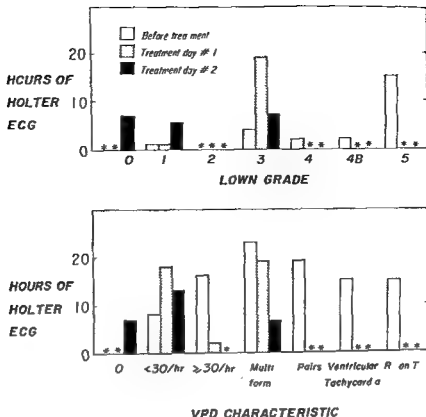


Fig 4 The use of the Lown grading system to summarize the results of an antiarrhythmic drug trial with unipramine. Above the Lown system is used to summarize the findings in three 24 hour Holter ECG recordings: tape 1 = pretreatment, tape 2 = lower dose, and tape 3 = higher dose. Below the same three tapes have been summarized by tabulating all hours containing the VPD characteristic. Only the frequently characteristics are mutually exclusive. An asterisk indicates that the Lown grade or the VPD characteristic was not present in any hour of the recording. The Lown grades do not accurately reflect the hourly count for VPD characteristics (see below) and do not accurately reflect the response of VPD characteristics to therapy.

the number of hours in the 24 hour ECG recording which is assigned to that grade. Subscripts further characterize some Lown grades: for grade 2 the subscript gives the number of VPDs in the grade 2 hours; for grade 3 the subscript denotes the maximum number of VPD configurations observed in any single grade 3 hour; for grade 4A the subscript gives the maximum number of VPD pairs in any grade 4 hour; for grade 4B the first subscript refers to the maximum number of episodes of ventricular tachycardia in a single grade 4B hour while the second subscript indicates the number of cycles in the longest run of ventricular tachycardia; for grade 5 the subscript identifies the maximum number of R on T VPDs occurring in any grade 5 hour.

The Lown equation has several ambiguities and drawbacks. First no account is given of the noise that frequently occurs in ambulatory ECG recordings. Noise reduces the VPD count and if an adjustment is not made the calculated VPD

frequency will be too low. Noise also increases the likelihood of false positive VPDs. Both of these effects make noise important to report. Second the equation makes it difficult to determine VPD frequency or other VPD characteristics. In the Lown grades a subscript applies only to the hours assigned to its grade.¹² Thus if five VPD configurations exist in a 24 hour ECG recording but only two appear in any grade 3 hour the subscript for grade 3 will be 2 not 5. Similarly the subscript to grade 2 does not count the VPDs occurring in higher grades. This convention makes it impossible to calculate VPD frequency for a 24 hour ECG recording. Third is given for grade 1 therefore the VPDs in Lown grade 1 hours.

To illustrate the use of intervention trials we and individual VPD in ambulatory ECG recording undergoing anti

Pacing and sensing thresholds can then be determined during tachycardia. Several burst patterns can be tested and the most effective one determined.

We feel pacing has significant advantages when compared with pharmacologic therapy. With antiarrhythmic drugs, adverse effects are common frequently resulting in significant morbidity and occasional death. The patient is freed from the nuisance of taking multiple doses of medication each day. Pacing may be an especially effective form of therapy for those patients who are unreliable. Pacing for supraventricular arrhythmias of course carries some complications as well. It requires a surgical procedure for implantation and carries with it all the usual complications of pacemaker implantation. In addition, patients treated in this way are at risk of the induction of atrial fibrillation which if persistent may require cardioversion.

This pacemaker provides safe and effective therapy for supraventricular tachyarrhythmias. It is most applicable in those patients unresponsive to pharmacologic therapy, unaware of the presence of supraventricular arrhythmias and/or rapidly disabled by their tachycardias. Tachycardia therapy with the automatic tachycardia terminating pacemaker has a high level of patient acceptance due to the freedom from the expense, side effects and nuisance of drug therapy.

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ramine (Fig 4) Fig 4 permits a comparison of the number of hours assigned each Lown grade (above) to the actual number of hours containing each VPD characteristic (below) Prior to treatment the patient has Lown grade 5 in 15 of the 24 hours recorded Lown grades 4A and 4B occur in 2 hours each although in reality VPD pairs occur in 19 hours and ventricular tachycardia in 15 hours There are 4 hours in Lown grade 3 although the patient actually has multiform VPDs in all but 1 hour of the 24 hour record There are no Lown grade 1 hours however VPDs are more frequent than 30/hour during 16 of the 24 hours in the pretreatment tape This disparity is accounted for by the strong association between a VPD frequency of ≥ 30 /hour and complex VPD features Because of this association the Lown equation provides almost no information concerning VPD frequency in the pretreatment record

Analysis of the response to imipramine therapy (Fig 4) shows that the Lown grading system is also inadequate for judging the efficacy of antiarrhythmic therapy Imipramine markedly decreases both VPD frequency and complex VPD features (Fig 4 bottom) The Lown grades (Fig 4 top) do not accurately reflect this response of VPD frequency and VPD complexity to imipramine For example Lown grade 3 hours increase during the first day of imipramine therapy (Fig 4 top) even though there is a progressive decrease in the hours containing multiform VPDs (Fig 4 bottom) Similarly grade 2 hours show no change even though hours with frequent VPDs (≥ 30 /hour) decrease markedly on the first day of imipramine treatment and then disappear entirely Thus the Lown grading system may provide only limited insight into the magnitude or even the direction of the response of individual VPD characteristics to antiarrhythmic therapy

We contend that a few simple modifications of the Lown arrhythmia equation provide a much more valuable tool for evaluating the response of ventricular arrhythmias to therapy We recommend the following changes (1) count the actual VPD characteristics rather than Lown grades (2) count each complex VPD feature independent of VPD frequency or any other complex VPD features and (3) use subscripts for VPD characteristics that apply to all hours of the ECG recording We replace Lown grades 0 1 and 2 with a single frequency category F The first superscript (prehyphen) for F is the number of

consecutive hours of ECG analyzed the second (posthyphen) superscript shows the hours of data lost due to noise in the hours analyzed The subscript for F is the average hourly VPD frequency for all hours analyzed (adjusted for noise) This new notation (1) clearly indicates 24 hour average VPD frequency (2) avoids dichotomizing at an arbitrary frequency value (3) condenses all frequency information into a single category and (4) accounts for data loss due to noise Accounting for data loss permits the investigator to correct the observed counts in all categories We have replaced Lown grades 3 4A 4B and 5 with M P V and R respectively M for multiform P for VPD pairs V for ventricular tachycardia and R for R on T VPD In our notation superscripts represent a count of all hours in which the VPD characteristic occurs The subscript to M is the number of different VPD configurations on the entire ECG recording and the subscripts to P V and R refer to the total number of these events in the ECG record We use a second subscript to R to give the shortest V/Q/T interval in the ECG recording

To compare our notation to the Lown arrhythmia equation we compared the three ECG records in Fig 4

Lown arrhythmia equation

| | | | | | | | |
|----------------|----|---|-----------------------------|------------------------------|------------------------------|--------------------------------|-------------------------------|
| Pretreatment | 0* | 1 | 2 ₀ ⁰ | 3 ₃ ³ | 4A ₇ ¹ | 4B ₆₋₃ ¹ | 5 ₁₅ ²⁴ |
| Treatment No 1 | 0* | 1 | 2 ₀ ⁰ | 3 ₁₉ ³ | 4A ₀ ⁰ | 4B ₀ ⁰ | 5 ₀ ⁰ |
| Treatment No 2 | 0 | 1 | 2 ₀ ⁰ | 3 ₂ ² | 4A ₀ ⁰ | 4B ₀ ⁰ | 5 ₀ ⁰ |

Modified arrhythmia equation

| | | | | | |
|----------------|-------------------------------------|------------------------------|---------------------------------|----------------------------------|-------------------------------------|
| Pretreatment | F ₃₄₋₂₁ ¹⁵ | M ₃ ²³ | P ₁₉ ¹⁶⁰⁴ | V ₁₅₄₋₆ ¹⁵ | R _{171-0.20} ¹⁵ |
| Treatment No 1 | F ₃₀₋₀₋₄ ^{13.3} | M ₃ ¹⁹ | P ₀ ⁰ | V ₀ ⁰ | R ₀ ⁰ |
| Treatment No 2 | F _{29-2.3} ^{4.3} | M ₂ ² | P ₀ ⁰ | V ₀ ⁰ | R ₀ ⁰ |

The subscript of the F category (average VPDs per hour) in our notation accurately shows the pronounced drop in VPD frequency during imipramine therapy whereas the Lown equation does not Our notation permits rapid calculation of the total number of VPDs (F superscript multiplied by F subscript) The Lown arrhythmia equation does not permit calculation of average VPD frequency or of total VPDs in an ECG recording Our notation reveals the progressive decrease in multiform VPDs during treatment Lown grade 3 does not reveal this response Also our notation clearly enumerates the repetitive activity in the ECG recordings whereas Lown grades 4A and 4B do not For these reasons we feel that the modi-

The Lown grading system is a better tool for the study of ventricular arrhythmias than the Lown grading system. It is more comprehensive and understandable as it takes into account all of the factors which can importantly modify ventricular arrhythmias. Neither the Lown grading system nor our notation permits a study of the hour-by-hour occurrence of ventricular arrhythmias for the pretreatment ECG shown in Fig. 4 and in the pretreatment arrhythmia equation. There is an obvious decrease in VPD frequency and complex VPD forms during sleep which cannot be appreciated when the data are displayed without the dimension of time. The timing of ventricular arrhythmias (Table IV), especially the relationship of ventricular arrhythmias to times of peak and trough serum drug levels can be crucial in determining a successful antiarrhythmic drug dose and dosing interval. If significant ectopy persists in a 24 hour ECG recording after initiation of antiarrhythmic drug therapy, the relationship of the residual ectopy to drug dose, to dosing interval, and to activity should be carefully evaluated. For this purpose, the tabulations that include the dimension of time (such as Table IV) are superior to the exposition of data in an arrhythmia equation.

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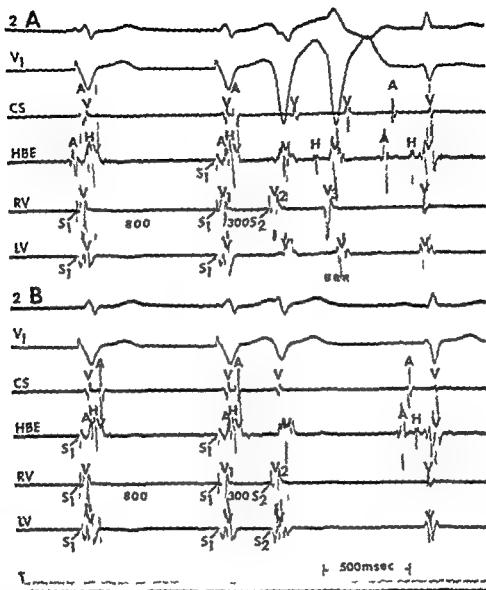


Fig 6 Pre-emption of bundle branch reentry by simultaneous right and left ventricular stimulation. The figure is organized as Fig 4. In panel A, a right ventricular premature stimulus (S₁) is delivered at a coupling interval of 300 msec during ventricular pacing (S-S) at a cycle length of 800 msec, resulting in bundle branch reentry (BBR) as previously described. In panel B, simultaneous right and left ventricular stimulation at the same coupling intervals as in panel A failed to induce BBR. Simultaneous stimulation of the opposite ventricle renders the retrograde limb of the BBR pathway (LV conduction system) refractory, thereby abolishing reentry.

of the patients with documented ventricular tachycardia/fibrillation had only bundle branch reentry.

Characteristics of repetitive ventricular reponses. Bundle branch reentry usually had a configuration similar to the ventricular paced complex that initiated this response at longer coupling intervals (i.e., right bundle branch block pattern for left ventricular premature stimuli and

left bundle branch pattern for right ventricular premature stimuli) (Figs 1 and 4). However, changes in morphology were observed at very close coupling intervals. Regardless of the ventricle of stimulation, bundle branch reentry occurred only when a critical degree of V-H delay was attained. The range of retrograde His-Purkinje conduction delay (V-H interval) required for initiation was as long as 160 to 300 msec. In most

Table II

| | VT/VF (58 pts) | RBBB (35 pts) | LBBB (17 pts) |
|------|-------------------|------------------|------------------|
| BBR | 29 | 2 | 1 |
| IVR | 43 | 20 | 8 |
| None | 8 | 14 | 8 |

BBB = bundle branch block R = right L = left BBR = bundle branch reentry IVR = intraventricular reentry VT/VF = ventricular tachycardia/ventricular fibrillation

patients demonstrating bundle branch reentry this response was elicited with a single premature ventricular stimulus during ventricular pacing in 11 patients (5%) double premature ventricular stimuli were required

The degree of retrograde His Purkinje conduction delay produced during ventricular stimulation was the same in patients who developed bundle branch reentry as in those who failed to develop this phenomenon The presence or absence of organic heart disease was not related to the appearance of retrograde conduction delay However retrograde conduction delay was only noted in 12 of the 35 (34.3%) patients with right bundle branch block and was observed in 296 patients (85%) without conduction delay

There was a direct relationship between paced cycle length and the coupling interval of bundle branch reentrant complexes This was related to a longer His Purkinje refractory period at the longer paced cycle length therefore facilitating the development of retrograde His Purkinje delay in response to ventricular extrastimuli No bundle branch reentry was observed during retrograde gap phenomena In addition bundle branch reentry did not occur when spontaneous or stimulated supraventricular complexes pre excited the His bundle antegradely prior to the time it would have been engaged retrogradely during ventricular extrastimuli (Fig 5) or when ventricular extrastimuli were delivered simultaneously in both ventricles (Fig 6) Bundle branch reentry produced one to four extra complexes but was never sustained

In contradistinction to responses due to bundle branch reentry intraventricular reentrant complexes appearing after single (63 patients 81%) or only after double ventricular extrastimuli (15 patients 19%) frequently had a configuration distinctly different from that of the paced ven-

tricular complex Intraventricular reentry occurred in the absence of definite retrograde H₁ potentials in approximately 80% of patients with these responses, and with H V intervals shorter than those in sinus rhythm in the remainder (16 patients) Intraventricular reentry most often occurred during stimulation within 25 msec of the ventricular refractory period however in 20 patients with ventricular tachycardia or ventricular fibrillation there was a zone of at least 50 msec prior to ventricular refractoriness when the intraventricular reentrant complexes were noted In patients who subsequently developed sustained ventricular tachycardia the intraventricular reentrant complex resembled the configuration of the complexes during ventricular tachycardia regardless of the site of stimulation (Fig 2) In three patients ventricular tachycardia was only inducible with programmed electrical stimulation of the left ventricle In these three patients intraventricular reentrant complexes were only elicited with left ventricular stimulation and occurred with right bundle branch block morphologies Supraventricular stimuli did not prevent intraventricular reentry nor did biventricular stimulation prevent it in ten patients in whom these perturbations were attempted

In patients who demonstrated both bundle branch reentry and intraventricular reentry the zones of coupling intervals which produced each were different although some overlap appeared In ten cases bundle branch reentrant complexes acted as a secondary ventricular premature extrastimulus inducing intraventricular reentry When this was observed the bundle branch reentry occurred at coupling intervals similar to those found capable of inducing intraventricular reentry with double premature ventricular extrastimuli In seven patients intraventricular reentry was associated with the appearance of unrelated retrograde His potentials

Of the 19 patients who had ventricular fibrillation prior to study four had no demonstrable organic cardiac disease, only one of these four had intraventricular reentry and this patient was the only one of the four with inducible ventricular fibrillation Of the 15 patients with heart disease and ventricular fibrillation 11 had intraventricular reentrant complexes eight of these 11 had inducible ventricular fibrillation In each case these intraventricular reentrant complexes were

branch block morphology rarely developed bundle branch reentry.^{1,4} This appears to reflect prolonged retrograde as well as antegrade conduction and refractoriness.^{1,4,7} However, a higher than expected percentage of patients with bundle branch block developed intraventricular reentry (55% versus 19%). Therefore not surprisingly, a high incidence of ventricular arrhythmias has been reported in patients with such conduction disturbances, and ventricular fibrillation rather than heart block has been suggested as the cause of sudden death in many of these patients.^{8,9} These relationships provide further support that intraventricular reentry is a marker for those patients prone to develop malignant ventricular tachyarrhythmias.

In conclusion two different mechanisms of repetitive ventricular responses encountered during ventricular stimulation exist. One bundle branch reentry involves a macroreentrant circuit involving the bundle branches and is a benign phenomenon occurring in more than half the patients in whom ventricular stimulation is carried out. Intraventricular reentry on the other hand represents a pathological event closely related to clinical ventricular arrhythmias.

Summary

Repetitive ventricular responses (RVR) to programmed ventricular stimulation were observed in 238 of 400 patients (59.5%). Two types of RVR with different mechanisms and clinical significance in relation to ventricular arrhythmias could be identified:

1 Repetitive ventricular responses resulting from bundle branch reentry occurred in 53% of patients without any significant difference of incidence in the presence (52.9%) or absence (54.1%) of organic heart disease.

2 Repetitive ventricular responses resulting from intraventricular reentry occurred in 19.5% of patients with a significantly higher incidence in patients with (23.9%) than without (8.1%) organic heart disease. Thirty-eight of 41 (92.7%) patients with inducible ventricular tachycardia or fibrillation also had intraventricular reentry but only 9.1% of patients without these arrhythmias manifested intraventricular reentry ($p < 0.005$). Moreover the mode of induction and the configura-

tion of intraventricular reentry was closely related to that of ventricular tachycardia when induced.

It is concluded that bundle branch and intraventricular reentry are different phenomena both in mechanism and relationship, to spontaneous ventricular arrhythmias. Bundle branch reentry appears to be a benign phenomenon which represents a physiological response of the His-Purkinje system and is not directly related to ventricular arrhythmias. On the other hand our data suggest that intraventricular reentry may be a 'pathologic' phenomenon closely related to ventricular arrhythmias. The presence of intraventricular reentry may identify patients who are prone to develop ventricular tachycardia or fibrillation.

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multiple (\geq three complexes) and were often polymorphic resembling so called *torsade de pointe*.

Of the 39 patients who had sustained ventricular tachycardia nine had no organic cardiac lesion only four of these nine patients had inducible ventricular tachycardia and three of these four had intraventricular reentries. Of the 30 patients with known cardiac disease 28 had inducible ventricular tachycardia and 26 of these 28 had intraventricular reentries. Intraventricular reentry did not necessarily occur at the same drive cycle length ($S_1 S_1$) that was utilized during induction of ventricular tachycardia and reentrant complexes occurred with single extrastimuli in five patients who required double ventricular extrastimuli for initiation of ventricular tachycardia. Two patients with noninducible ventricular tachycardia also had intraventricular reentry. Conversely of 78 patients demonstrating intraventricular reentry 43 had documented spontaneously occurring sustained ventricular tachycardia or ventricular fibrillation 38 of these 43 had inducible ventricular tachycardia or fibrillation in the electrophysiologic laboratory as well.

Thirty five patients in this study had right bundle branch block pattern on their surface electrocardiogram all were in sinus rhythm. Only two of these patients demonstrated bundle branch reentry 21 however developed intraventricular reentrant complexes. Of 17 patients with left bundle branch block only one had bundle branch reentry and eight had intraventricular reentry.

Discussion

Repetitive ventricular responses are a frequent accompaniment of ventricular stimulation. Such repetitive responses were noted in 59.5% of 400 consecutively studied patients. The most common form of repetitive response was that due to bundle branch reentry. As suggested by previous workers¹ bundle branch reentry was observed in normal individuals as frequently as it was in those with organic heart disease. Wellens and colleagues² and Josephson and associates³ observed that bundle branch reentry rarely if ever caused sustained ventricular tachycardia and this was true in the present study in which no patient developed sustained bundle branch reentry as the mechanism of sustained ventricular tachycardia.

Thus macroreentry involving the bundle branches (the mechanism postulated for bundle branch reentry) does not appear to be a cause of sustained spontaneous or induced ventricular arrhythmias. However bundle branch reentrant complexes may act as additional extrastimuli inducing sustained ventricular tachycardia or intraventricular reentry. Wellens and co workers² observed that in six of 29 patients with inducible ventricular tachycardia the initial complex (V_1) was different in morphology from subsequent complexes and in some cases this initial complex was undoubtedly a bundle branch reentry.

Intraventricular reentry appeared far more commonly in patients with organic heart disease than in patients with normal hearts and was associated with the presence of more malignant forms of ventricular dysrhythmias. Of 78 patients with either isolated intraventricular reentry or intraventricular reentry associated with bundle branch reentry 43 had documented sustained ventricular tachycardia and/or fibrillation. Furthermore the frequency of intraventricular reentry in patients with significant ventricular arrhythmias was 74% whereas it was 9.1% in patients without such arrhythmias ($p < 0.001$). While the patient population with intraventricular reentry contained a higher percentage of patients with documented or suspected ventricular tachycardia/fibrillation the fact that this form of repetitive response especially when multiple was to a large extent confined to this group of patients suggests that a relationship between the two does exist.

Intraventricular reentry probably results from reentry within the ventricular myocardium and distal His Purkinje system. This may occur locally in proximity to the site of stimulation or at a distance and in relation to anatomic or ischemic lesions (especially in the left ventricle). Our data suggest that large segments of the proximal His Purkinje system are not required. Unlike bundle branch reentry intraventricular reentry cannot be prevented by appropriately timed supraventricular impulses which pre-excite the bundle of His. Furthermore the dissociation between His bundle electrograms and intraventricular reentrant responses suggests that the proximal His Purkinje system does not form a portion of the reentrant pathway.

As noted previously patients with bundle

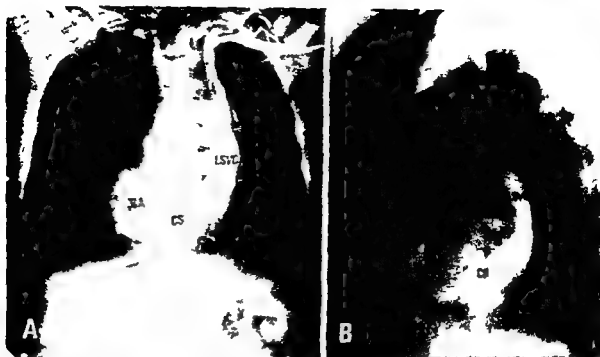


Fig 1 Biplane anpicardiograms of the PLSVC in a 23-year-old female patient with associated ASD. Panel A is the frontal view and panel B is the lateral view. The PLSVC is clearly demonstrated both in the frontal and lateral view of the chest. It runs along the left side of the sternum posterior to the left atrium as a narrow tubular shadow. Abbreviations: RA = right atrium; CS = coronary sinus; LSVC = left superior vena cava.

Table 1 Summary of the clinical, hemodynamic and echocardiographic findings in 12 patients with PLSVC

| No | Patients | Age | Sex | Complication | Cath. | LCG | AML | | AO | LA | LVDD | LVDs | LVO | RVO | EF (%) | Op |
|----|----------|-----|-----|------------------|-------|-----|---------|-------------|----|----|------|------|-----|-----|--------|----|
| | | | | | | | E (mm.) | DDR (mm/s.) | | | | | | | | |
| 1 | M. A. | 27 | F | ASD | + | + | 25 | 143 | 24 | 31 | 30 | 24 | 27 | 36 | 6 | + |
| 2 | M. M. | 24 | F | ASD | + | + | 20 | 110 | 17 | 32 | 32 | 20 | 30 | 37 | 82 | + |
| 3 | N. O. | 4 | F | ASD + MI + PAPVR | + | + | 23 | 98 | 13 | 33 | 30 | 24 | 26 | 39 | 6 | + |
| 4 | T. S. | 33 | F | MS | + | + | 24 | 29 | 28 | 34 | 30 | 30 | 24 | — | — | + |
| 5 | K. S. | 37 | M | ASD | + | + | 20 | 112 | 31 | 30 | 48 | 33 | 32 | 30 | 70 | + |
| 6 | K. M. | 8 | F | — | + | + | 18 | 103 | 21 | 21 | 41 | 28 | 24 | 21 | 6 | — |
| 7 | M. K. | 4 | M | PS + ASD | + | + | 19 | 130 | 17 | 23 | 33 | 20 | 22 | 27 | — | + |
| 8 | M. A. | 3 | F | TA | + | + | 27 | 115 | 30 | 30 | 56 | 47 | 36 | 27 | 41 | + |
| 9 | — | — | F | ASD | + | + | 20 | 103 | 15 | 18 | 32 | 24 | 20 | 29 | 70 | — |
| 10 | T. H. | 1 | M | ASD | + | + | 14 | 84 | 10 | 15 | 21 | 14 | 17 | — | — | + |
| 11 | T. H. | 4 | — | TF | + | + | 18 | 76 | 23 | 16 | 25 | 16 | 22 | 10 | 74 | + |
| 12 | N. H. | 14 | F | ASD | + | + | 2 | 98 | 23 | 20 | 34 | 30 | 27 | 24 | 67 | + |

Abbreviations: Cath = catheterization; LCG = ultrasonocardiogram; Tomo = cross-sectional echocardiogram; AML = anterior mitral leaflet; E = amplitude; DDR = diastolic deceleration rate; AO = aorta; LA = left atrium; LVDD = left ventricular diastolic dimension; LVDs = left ventricular systolic dimension; LVO = left ventricular outflow tract; RVO = right ventricular outflow tract; EF = ejection fraction; Op = cardiac operation; PAPVR = partial anomalous posterior vena cava return; TF = tetralogy of Fallot; TA = tricuspid atresia; ASD = atrial septal defect; MP = mitral regurgitation; M = mitral; P = pulmonary stenosis.

diagrams of the heart was obtained by two methods: (1) a Polaroid camera or an ordinary 35 mm camera was used with a shutter speed of 1/10 sec or in synchrony with the QRS complex of the patient's electrocardiogram (ECG); (2) an 8 mm

movie camera was utilized for the continuous recording of the heart movement at 15 frames/sec.

The analysis of the cross-sectional echocardiograms was carried out on three cross-sections

Cross-sectional echocardiographic study on persistent left superior vena cava

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Persistent left superior vena cava (PLSVC) is essentially not a serious cardiac malformation producing severe cardiac symptoms by itself. However, if this lesion can be detected noninvasively, the burden on patients would be less at cardiac catheterization and surgical intervention. In addition, it would be possible to differentiate the abnormalities emanating from the left atrium and/or the boundary between the left ventricle and the left atrium noninvasively.

Echocardiography has proved to be useful to analyze the cardiac movement and anatomical abnormalities and to estimate the cardiac function in various congenital and acquired heart diseases. Echocardiographic findings of enlarged coronary sinus communicating with an anomalous vein have been reported by a few clinicians using M mode echocardiography, but the echo source of the coronary sinus was not fully analyzed. In addition, a study on PLSVC with cross-sectional echocardiography has yet to be reported. The purpose of this study is to describe our attempt at the noninvasive diagnosis of the PLSVC using high speed cross-sectional echocardiography with mechanical sector scanning combined with an M mode system.

Materials and methods

Twelve patients underwent high speed cross-sectional echocardiography with a real time mechanical imaging system. Ages ranged from 1 to 37 years. Four patients were male and eight were female. Cardiac catheterization combined with angiocardiography was performed on all 12 patients before or after cross-sectional echocardiographic examination. The main associated cardiac malformations of the examined patients are shown in Table I. Seven of the patients underwent surgical repair for main cardiac malformations, but the PLSVC was not operated on.

Cross-sectional and M mode echocardiograms were obtained using a Toshiba Model SSL 51H Sonolayergraph as previously reported by our laboratory. This instrument has a 3 MHz, 10 mm transducer focused at 75 mm, with a repetition rate of 36 kHz. Sector speed was 30 cross sections per second and sector angle was changed from 30 degrees to a maximum of 90 degrees, but it was usually observed with the fixed angle of 80 degrees. To enable the identification of the echo source, a certain scanning line was manually selected and B mode was switched to M mode to obtain the M mode echocardiogram.

The patients were examined in the supine position. The transducer was immersed in a castor oil bath placed on the chest surface over the third or the fourth intercostal space at the left sternal border. The so-called proximity-immersed method was employed.*

The recording of the cross-sectional echocar-

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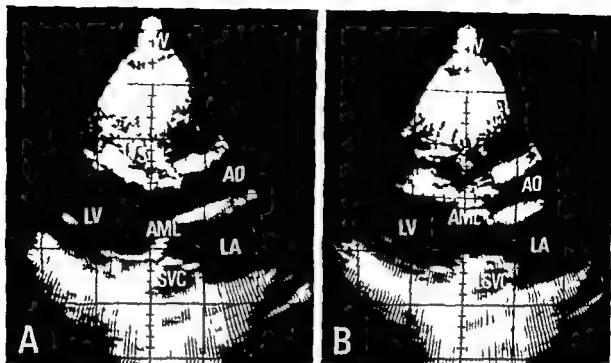


Fig 3 Cross sectional echocardiograms of a long cardiac axis in a 24 year old female patient having PLSVC with ASD. Panel A is an image of systole and panel B is recorded in early diastole. An unusual circular echo is recognized at the boundary between the left atrium and the left ventricle. Its circular echo shows an almost complete round form. Abbreviations: CW = chest wall, RV = right ventricle, IVS = interventricular septum, AO = aorta, LA = left atrium, LV = left ventricle, AML = anterior mitral leaflet, SVC = left superior vena cava.

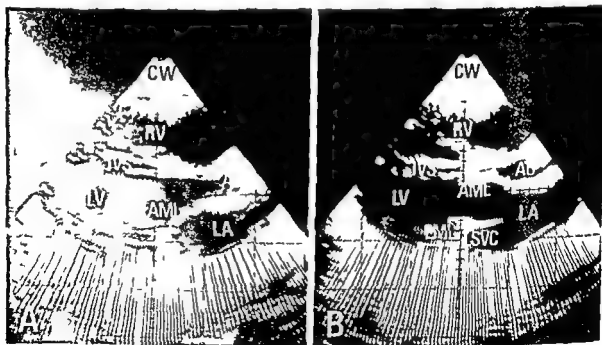


Fig 4 Cross sectional echocardiograms in the long cardiac axis in a 4 year old female patient having PLSVC with ASD and MI. Panel A is recorded in systole and panel B in diastole. The circular echo is presented posterior to the PML and it is larger in diastole than in systole. The echo discontinuity is recognized at the upper portion of the circular echo. Abbreviations: CW = chest wall, RV = right ventricle, IVS = interventricular septum, AO = aorta, LA = left atrium, LV = left ventricle, AML = anterior mitral leaflet, PML = posterior mitral leaflet, SVC = left superior vena cava.

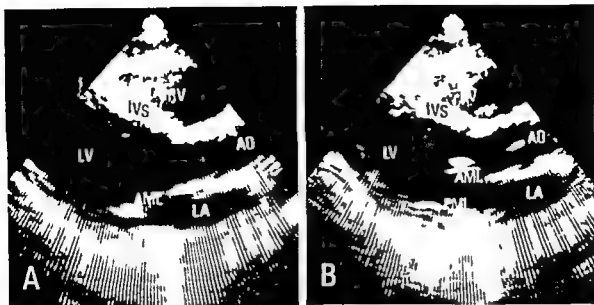


Fig 2 Cross sectional echocardiograms along the long cardiac axis in a normal subject. Panel A is recorded in systole and panel B shows the early diastolic image of the heart. The posterosuperior region of the PML is solid wall tissue and revealed no abnormal findings. Abbreviations: RV = right ventricle, AO = aorta, IVS = inter ventricular septum, AML = anterior mitral leaflet, PML = posterior mitral leaflet, LA = left atrium, LV = left ventricle.

along the long cardiac axis, the sagittal and the horizontal planes of the chest. In some patients only one or two cross sections were analyzed.

Results

Fig 1 shows the biplane angiocardigrams obtained by the injection of the contrast material from the left subclavian vein in patient No 2 having PLSVC associated with ASD. The PLSVC is demonstrated posterior to the left atrium along the left side of the sternum as a narrow tubular image and it opens to the enlarged coronary sinus in the right atrium. Thus the PLSVC seems to run along the left atrioventricular sulcus.

The cross section of the long cardiac axis demonstrated the relationship between the aorta and two left sided heart chambers. The posterior region of the posterior mitral leaflet (PML) usually appears as a solid wall echo in the normal subject (Fig 2). No abnormal echo was recognized at this region.

In the patients with PLSVC a circular echo was recognized at the boundary between the left atrium and the left ventricle in the cross section of the long cardiac axis. Fig 3 shows the cross sectional echocardiograms along the long cardiac axis in a 24 year old female having PLSVC with ASD. A circular echo having an echo free space is clearly demonstrated at the posterosuperior

region of the PML. In this patient the circular echo has an almost complete form without echo discontinuity. According to the real time observation a circular echo was gradually enlarged during systole and it was largest in early diastole at the E point of the anterior mitral leaflet (AML) and contracted in mid diastole. In a 4 year old girl with PLSVC the circular echo was also recognized in the same region as in Fig 3 (Fig 4). However the upper part of this echo seems to show an echo discontinuity and to open into the left atrium. In the majority of the examined patients the echo discontinuity was recognized at the upper part of the circular echo. It is most likely that the echo discontinuity occurred because the echo beam went parallel to the wall of the PLSVC.

When the scanning line was selected to the circular echo to obtain the M mode echocardiogram an unusual linear echo with the shallow space was recorded behind the AML. Fig 5 presents the M mode scan echocardiograms obtained from patients No 1, 2, 3 and 4. The AML shows almost normal movement and the diastolic descent rate (DDR) of the AML was also within normal limits. The unusual linear echo was demonstrated posterior to the AML but it appeared neither in the left ventricle nor in the left atrium. Thus linear echo gradually moved

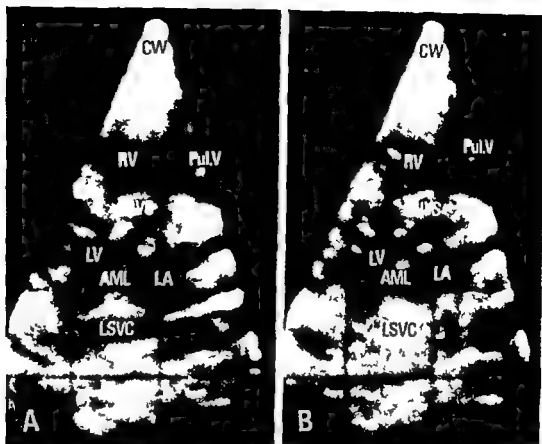


Fig 6 Cross sectional echocardiograms in the patients with PLSVC before (A) and after (B) dye injection. These pictures were recorded along the cross section of the sagittal plane of the chest. An echo free space is recognized posterior to the two left sided heart chambers before dye injection (A) but the positive contrast echo appears in its echo free space after injection of the indocyanine green from the left medial cubital vein (B). Abbreviations: CW = chest wall, Pul V = pulmonary valve, RV = right ventricle, IVS = interventricular septum, LA = left atrium, AML = anterior mitral leaflet, LV = left ventricle, LSVC = left superior vena cava.

and echocardiographic findings of 12 patients. The DDR of the AML was within normal limits except for patient No. 5 who had mitral stenosis. The amplitude of the AML and aortic dimension (AOD) were both in the normal range. The right ventricle was enlarged in the patients with ASD. The left atrial dimension (LAD) was mildly enlarged in patients with mitral stenosis and mitral regurgitation. An unusual linear echo was recorded in all patients by M mode echocardiography.

Discussion

Recently cross sectional echocardiography has developed in various forms as a mechanical and electronic scanning system.¹ These methods have made it possible to demonstrate the anatomical abnormalities and to observe the movement of the heart in real time. The high speed mechanical sector scanning system reported previously

by our laboratory can also be used to observe cardiac movement and the anatomical abnormalities in real time.

In general the PLSVC was situated at the posteromedial region to the left atrium and opened to the coronary sinus in the right atrium. It was clearly demonstrated in the angiograms as a narrow tubular image and was located at the left atrioventricular sulcus.

Echocardiographic findings of the PLSVC have not been reported, but a few studies on enlarged coronary sinus were presented by other authors.^{2,3} There has also been no documentation on the cross sectional echocardiographic features of the PLSVC and the enlarged coronary sinus.

In our study a circular echo with an echo free space and a tubular echo were recorded at the posteromedial region of the mitral valve in the cross section of the long cardiac axis and the sagittal plane of the chest. All of the 12 patients

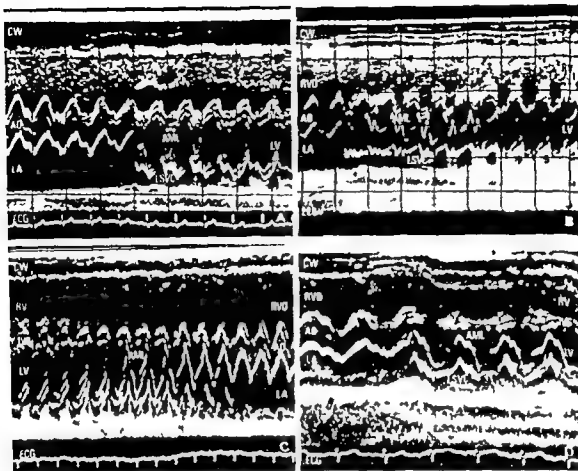


Fig 5 M mode scan echocardiograms in the patients with PLSVC when the transducer was rotated from the aorta to the left ventricle or from the left ventricle to the aorta. These pictures were recorded from patients No 1 2 3 and 6 respectively. These patients show the abnormal linear echoes posterior to the AML. Their movement pattern is slightly changed respectively. But these echoes move anteriorly during systole and go back posteriorly in mid diastole. An echo free space is recognized posterior to its linear echo. Abbreviations: CW = chest wall, RV = right ventricle, AO = aorta, LV = left ventricle, AML = anterior mitral leaflet, RVOT = right ventricular outflow tract, LA = left atrium, LSVC = left superior vena cava, ECG = electrocardiogram.

anteriorly during systole and retreated posteriorly in diastole. Occasionally its movement pattern was similar to that of the AML in some cases. It was not considered as an echo of the PML nor as the posterior wall of the left ventricle (LVPW) or that of the left atrium (LVPW) due to the movement and the location. Its abnormal linear echo was not detectable in normal subjects and in patients without PLSVC. If this echo emanates from the solid tissue, the echo free space would not be demonstrable.

In the cross sectional echocardiogram through the sagittal plane of the chest, a narrow tubular echo was also recognized at the posterior region of the two left sided heart chambers (Fig 6A). It was considered to be neither a part of the left ventricle nor the left atrium. When the transducer

was rotated from the sagittal cross section of the chest to the long cardiac axis, it seemed that the circular and tubular echoes emanated from the same lesion.

In patient No 2, an injection of indocyanine green was given in the left median cubital vein to confirm the source of the circular echo. On the injection of dye, the usage of the PLSVC was clearly demonstrated as the tubular echo in the sagittal plane of the chest (Fig 6A). About one minute after the venous injection, the positive contrast echoes appeared in the abnormal cavity (Fig 6B). But the upper half was not filled with a cloud of indocyanine green. This contrast echo appeared neither in the left ventricle nor in the left atrium.

Table I summarizes the clinical hemodynamic

whereas it appeared neither in the left atrium nor in the left ventricle. This abnormal echo was not recognized in normal subjects and other cardiac diseases without PLSVC.

In M mode echocardiography, the unusual linear echo was recorded behind the AML. It moved anteriorly during systole and went back posteriorly in diastole.

Consequently because of the direction of the echo beam, the movement and the location of the unusual echo, it seems to emanate from the lower part of the PLSVC. High speed cross sectional echocardiography has proved to be useful for noninvasive diagnosis of the PLSVC.

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had the PLSVC opened to the coronary sinus in the right atrium and these abnormal circular and tubular echoes were recognized in all. According to the M mode echocardiograms this feature was also shown as an unusual linear echo showing an echo free space posteriorly. This is neither the echo of the LVPW nor that of the LAPW since it has an echo free space between the unusual linear echo and more dense structures of the heart wall.

It is a matter of controversy as to whether this echo resulting from the enlarged coronary sinus communicates with an anomalous vessel or with the PLSVC itself. Gramatik and Sahn¹ reported the echocardiographic findings of the enlarged coronary sinus. The same authors recognized an unusual linear echo behind the AML with an echo free space and they stressed that its linear echo moved posteriorly during systole with a resultant narrowing of space followed by a widening in diastole as the margin moved forward. In contrast our data showed that the linear echo was gradually enlarged during systole and the anterior margin retreated backward in mid diastole. The movement was different in their report and in ours.

In this study the transducer was placed at the left side of the sternum in the third or the fourth intercostal space and the echo beam was set to the posteromedial direction perpendicularly through the left atrioventricular sulcus. In addition the echo beam went through the left sided margin of the right ventricle and the right ventricle was demonstrated to be a small cavity in the cross section of the long cardiac axis. But the right atrium was not recognized in the same cross section. On the other hand the right ventricular outflow tract was observed in the cross section of the sagittal plane of the chest but the right atrium and coronary sinus were not recognized. However the circular and tubular echoes were clearly recognized posterior to the left sided heart chambers in these cross sections. Thus the abnormal echo was considered to emanate from the PLSVC.

The positive contrast echo appeared in the abnormal space behind the mitral valve with the injection of indocyanine green from the left median cubital vein. But its echo cloud was recognized neither in the left ventricle nor in the left atrium and the circular echo was not consid-

ered to derive from the left sided heart chambers. It was identified as PLSVC by the movement and the location of the unusual echo and with the contrast echocardiographic technique.

The abnormal echoes at the border between the left ventricle and the left atrium and/or in the left atrial chamber should be differentiated from those of PLSVC by echocardiographic examination but they are not always confirmable by M mode echocardiography alone. The abnormal echo from these regions was recognized as representing one of the following conditions: the posterior mitral leaflet and calcified mitral leaflet in mitral stenosis²; the diaphragm of the cor triatriatum³; the mass of the left atrial myxoma⁴; the linear or mass echo of the thrombus in the left atrium and thickened chordae tendineae⁵. Cross sectional echocardiography served to show a spatial orientation of the heart and these abnormal echoes were clearly observed at the original position. Therefore these echoes could be differentiated by this method through their different location, movement and characteristics.

High speed cross sectional echocardiography has proved useful to the noninvasive diagnosis of the persistent left superior vena cava.

Summary

Twelve patients with persistent left superior vena cava (PLSVC) were studied using high speed cross sectional echocardiography with mechanical sector scanning. The majority of the examined patients had other associated congenital heart diseases.

A circular echo with an echo-free space was demonstrated at the posterosuperior region of the posterior mitral leaflet (PML) in the cross section of the long cardiac axis. It was also recognized as a narrow tubular cavity echo posterior to the left atrium and the left ventricle in the cross section of the sagittal plane of the chest. This abnormal echo was gradually enlarged during systole and the unusual cavity was largest in early diastole at the E point of the anterior mitral leaflet (AML) and its anterior margin moved back in mid diastole. This abnormal echo seems to be correspond to the left atrioventricular sulcus. By the injection of indocyanine green at the left median cubital vein the positive contrast echo appeared in the cavity which was considered to be PLSVC.

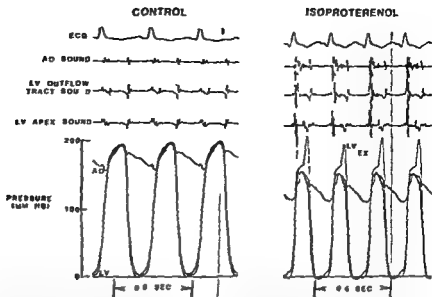


Fig 1 Sound and pressure in the aorta (AO) left ventricular (LV) outflow tract and LV apex during the control period and during the infusion of isoproterenol. During isoproterenol a gradient appeared between the LV apex and outflow tract. There was no intraventricular murmur but a murmur did develop distal to the aortic valve.

French angiographic catheter tip micromanometer was positioned in the outflow tract of the left ventricle. All catheters were made equisensitive.

Intracardiac pressure and sound were measured with the same catheter tip transducer as was previously described in detail.⁶ Pressure and sound were recorded on an Electronics for Medicine VR 12 photographic recorder at paper speeds of 25 and 250 mm/sec. The frequency response of the recording system was flat to 700 Hz with a 3 dB drop at 2100 Hz.

A left ventriculogram was obtained with the dog on its left side following the measurement of control pressures and sound. Pressures and sound measurements and the ventriculogram were repeated after an intraventricular pressure gradient (> 30 mm Hg) was induced by a constant intravenous infusion of isoproterenol (4 to 8 μ g/minute). All ventriculograms were obtained on 35 mm cine film at 60 frames/second.

In two dogs intentional entrapment of the tip of the catheter was induced by wedging the catheter in the ventricular trabeculae.

Results

Intracardiac measurements of pressure and sound showed no intraventricular pressure gradient or murmurs during the control period. The left ventriculogram of all dogs during the control

state showed good contraction and no mitral regurgitation.

Following the infusion of isoproterenol, an intraventricular pressure gradient that ranged between 47 and 90 mm Hg developed in all dogs. No systolic or diastolic murmurs were detected within the left ventricle. An ejection murmur was recorded above the aortic valve in all but one dog (Fig 1). The left ventriculogram performed during the infusion of isoproterenol showed almost complete obliteration of the apical region of the left ventricle.

In two dogs in which entrapment of the tip of the catheter was induced, an intraventricular gradient of 80 mm Hg was observed. The left ventriculogram showed a normally contracting left ventricle. Recordings of intracardiac sound in both dogs showed no murmurs in the left ventricle or distal to the aortic valve.

Discussion

In this study we observed no intraventricular murmur in the obliterating left ventricle despite a prominent intraventricular pressure gradient. When a systolic murmur occurred it was distal to the aortic valve. These intracardiac sound recordings were strikingly different from those observed in patients with hypertrophic obstructive cardiomyopathy.⁷⁻¹² Studies in patients with true ob-

Intracardiac phonocardiography in experimental left ventricular cavity obliteration potential clinical applicability for the distinction of obliterating left ventricle from hypertrophic obstructive cardiomyopathy

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Left ventricular cavity obliteration may be seen in a spectrum of ventricular disease states. It is important to distinguish it from outflow tract obstruction particularly hypertrophic obstructive cardiomyopathy which it may simulate because of differences of treatment. The similarity of the clinical features and the hyperdynamic nature of ventricular contractions that are common to both hypertrophic obstructive cardiomyopathy and left ventricular outflow tract obstruction increases the difficulty of differentiation. An intraventricular pressure gradient is generally considered an important diagnostic feature of hypertrophic obstructive cardiomyopathy and other forms of outflow tract obstruction. However an intraventricular pressure gradient also occurs in left ventricular cavity obliteration. An intraventricular pressure gradient can also appear when the catheter is entrapped in cardiac trabeculae.

Because an intraventricular pressure gradient may not actually reflect an outflow tract obstruction

it has been suggested that the presence of an intraventricular pressure difference not be accepted as proof of an obstruction without unequivocal proof by other means. In view of this other methods for distinguishing between an intraventricular pressure gradient produced by an outflow tract obstruction and a gradient produced by cavity obliteration would be useful. We have previously shown that intracardiac sound is useful for identifying subvalvular stenoses and determining the validity of subvalvular pressure gradients in hypertrophic obstructive cardiomyopathy, subvalvular tunnel stenosis and subvalvular membrane. The purpose of this investigation is to describe intracardiac phonocardiography in dogs in which left ventricular cavity obliteration was induced by drugs and to explore the potential use of intracardiac phonocardiography for distinguishing left ventricular cavity obliteration from left ventricular outflow tract obstruction.

Methods

Intracardiac pressure and sound were measured in six closed chest mongrel dogs anesthetized with 25 mg/kg intravenous injections of sodium pentobarbital and ventilated with room air. A No. 6 French catheter tip micromanometer was positioned approximately 1 cm distal to the aortic valve. A second No. 6 French catheter tip micromanometer was passed retrograde across the aortic valve and positioned as close as possible to the apex of the left ventricle while a No. 7

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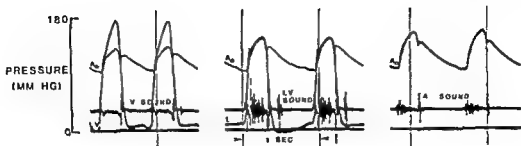


Fig 2 Intracardiac sound aortic (Ao) pressure and left ventricular (LV) pressure in a patient with hypertrophic obstructive cardiomyopathy. Left LV catheter was in the apex. Center LV catheter was within the outflow tract. Right Both micromanometers were within the aorta. The maximal intensity of the murmur occurred within the outflow tract (Reproduced from *Henry Ford Hosp Med J* 26:30, 19/8 by permission.)

flow tract obstruction (whether due to hypertrophic obstructive cardiomyopathy, a subvalvular membrane, or a tunnel stenosis) showed that the systolic murmur was of maximal intensity in the outflow tract of the left ventricle distal to the intraventricular obstruction¹¹ (Fig 2). The subvalvular murmurs were readily detected even when the gradients were small¹².

A pressure gradient measured within the left ventricle may be insufficient to establish a diagnosis of hypertrophic obstructive cardiomyopathy because left ventricular cavity obliteration or catheter entrapment may also cause an intraventricular gradient. Therefore additional evidence to support the diagnosis is needed. Intracardiac sound may furnish a significant clue to the identification of a true outflow tract obstruction and assist in distinguishing it from cavity obliteration. In ventricular cavity obliteration the systolic murmur when present is located distal to the aortic valve and not in the outflow tract of the left ventricle. Therefore distinction between true outflow tract obstruction and left ventricular obliteration can be made when simultaneous recordings of intracardiac pressure and sound are made.

The murmur generated in dogs with left ventricular cavity obliteration occurred distal to the aortic valve. Valvular leaflets act as projections into the stream of flow during systole³. This results in the breakdown of laminar flow³. Turbulence distal to the aortic valve would be greatly accentuated in the obliterating ventricle due to the increased blood velocity during ejection^{1, 13}.

Summary

Intracardiac sound was measured in six dogs, four with left ventricular cavity obliteration

induced by isoproterenol and two with catheter entrapment. In left ventricular cavity obliteration no murmur occurred within the left ventricle. Whenever a systolic murmur occurred it was distal to the aortic valve. In entrapment no murmur occurred within the left ventricle or distal to the aortic valve. Previous studies in patients with hypertrophic obstructive cardiomyopathy showed that the systolic murmur was of greatest intensity within the left ventricular outflow tract. Therefore intracardiac phonocardiography may assist in differentiating these conditions which produce an intraventricular pressure gradient.

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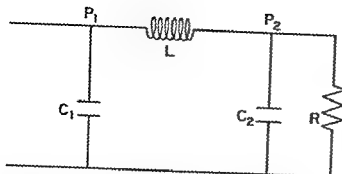


Fig 1 Third-order lumped parameter model (modified Windkessel) of the arterial system used in the pulse contour analysis. P_1 = proximal arterial pressure in mm Hg. P_2 = distal arterial pressure in mm Hg. C_1 = proximal compliance in ml/mm Hg. C_2 = distal compliance in ml/mm Hg. L = inertance in mm Hg/ml/sec. R = peripheral resistance in mm Hg/ml/sec.

Methods

Animal preparation and instrumentation

Eight mongrel dogs weighing from 11 to 30 kg were anesthetized with pentobarbital 25 mg/kg. A 16 gauge 2 inch Teflon catheter (Abbott Cath Abbott Laboratories 4535 16) was inserted percutaneously into the femoral artery and attached directly to a Bell and Howell 4 327 I strain gauge pressure transducer. Pressures were recorded on a Hewlett Packard 1064C recorder. The frequency response of the total system was flat in terms of amplitude to a frequency of 18 Hz. The amplitude began to rise at this point, peaked near 35 Hz, and fell rapidly for frequencies greater than 35 Hz. Heart sounds in a frequency range of 30 to 100 Hz and an ECG were also recorded. Duplicate cardiac outputs were measured by the dye dilution method using indocyanine green injected into the central venous circulation while arterial blood was withdrawn through a Gilford cuvette densitometer system. Drugs were administered through a short catheter in a foreleg vein.

Drug protocol. Propranolol was given to limit the heart rate change in response to the vasodilators. If initial heart rate was greater than 120 beats/minute, propranolol was given to reduce it to 120 beats/minute or until 0.5 mg/kg was given. If the heart rate was less than 120 beats/minute, 0.2 mg/kg was given. This was done in order to allow a diastolic interval long enough for a sufficient number of points to be sampled for use in the computation routine.

The experimental goal during the drug infusions was to infuse a dose that produced a prominent effect on the pressure curve but did not reduce arterial pressure below the physiologic

range. Sodium nitroprusside (NP) was administered by continuous infusion using a drop counter. Prominent effects on the curve shape within the limits of Equation 1 were generally seen with doses of from 2.5 to 10 $\mu\text{g/kg/minute}$ which produced pressure reductions of 20 to 30 mm Hg. Nitroglycerin (NTG) was given by continuous infusion on a weight basis. Data presented are from dosages of 5 to 10 $\mu\text{g/kg/minute}$. Hydralazine was given by bolus injection in a dose of 1 mg/kg. A 30 min period was allowed to reestablish baseline after NP and NTG. Hydralazine was given last since its effect is more persistent.

Data handling. Experimental data consisted of chart recordings of arterial pressures, the phonocardiogram, and cardiac outputs. Data were collected when pressure stabilized on NP after 10 minutes at the particular NTG dose used and 15 minutes after hydralazine injection.

Pressure waves were recorded using zero suppression so that pulse pressure covered the full range of the recording scale. This reduced the digitization error introduced by the semiautomatic analog to digital conversion done on a Graf/ Pen (Science Accessories Corporation Southport, Conn.) sonic digitizer. The digitization system has a resolution of 0.7 mm Hg. The output of the sonic digitizer went directly to an IBM 2100 digital computer. A sampling rate of 50 samples/sec was used. From each set of experimental data, three pulses were randomly selected, digitized, and averaged to form a composite curve that was used by the analysis program. The averaging procedure reduced noise levels introduced by the digitization process.

The analysis program utilized the portion of the pressure curve occurring after closure of the aortic valve, which is interpreted as the 'transient' response of the arterial system to the pressure change occurring in systole. This pressure signal was measured at the femoral artery, which was considered as point P in Fig 1. The second heart sound (S₂) was used as a reference in determining the starting point for this transient. Watt and Burrus began their analysis at S₂. This however does not take into account pulse wave velocity, which must be considered in femoral recordings from dogs, particularly when vasodilators are given. During these drug infusions we have observed S₂ occurring before the systolic peak in the femoral artery. A diastolic notch remnant on the descending systolic wave was not always visible to serve as a starting point. Consequently

Pressure pulse contour analysis in determining the effect of vasodilator drugs on vascular hemodynamic impedance characteristics in dogs

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Vasodilator drugs have been shown to be useful in the treatment of heart failure. Therapy results in a rise in cardiac output, reduction of peripheral resistance, and reduction of pulmonary wedge pressure.

A primary purpose of vasodilator therapy is improvement in pump function through a decrease in outflow impedance. The outflow impedance imposed by the arterial system consists of resistive, inertial, and compliant components. Systemic vascular resistance calculated from mean arterial pressure and cardiac output does not necessarily provide a valid index to absolute impedance or to changes in impedance. The impedance function described by Milnor is a frequency domain determination that requires measurement of instantaneous flow and pressure. A time domain approach would in theory also be valid and can be determined in a simplified manner by analysis of the pulse wave contour.

Watt and associates¹ have utilized an arterial pulse wave contour to analyze vascular properties in man. They observed that the diastolic part of

the pressure curve can be fit with a high degree of accuracy to the third order equation

$$P(t) = a_1 \exp(-a_2 t) + a_3 \exp(-a_4 t) \cos(a_5 t + a_6) \quad (1)$$

The a parameters from this equation describe the configuration of the arterial pressure contour in diastole. With knowledge of cardiac output, this configuration can be further interpreted using the electrical analog model shown in Fig 1.

This circuit is a lumped component model of the arterial system. It describes gross mechanical behavior considering the pressure wave after aortic valve closure as a decaying transient response. The model components C , L , C , and R cannot be equated with any specific vascular anatomy, but have physical meaning by analogy. R is the peripheral resistance as traditionally defined. C and C represent the lumped compliances of the proximal and distal arteries. L represents the lumped inductance that is found in the long columns of blood between the proximal and distal vessels of the arterial system. Watt and Burrus² found that very similar values for the model components were derived from pressure curves measured at various anatomical locations.

In the present study we have utilized the basic method of Watt and Burrus² to analyze the vascular effects of sodium nitroprusside, nitroglycerin, and hydralazine given systemically to normal dogs. The data reveal that these vasodilator drugs have different effects on the components that make up total vascular impedance.

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Work performed during tenure as a James F. Zagaria Memorial student fellow.

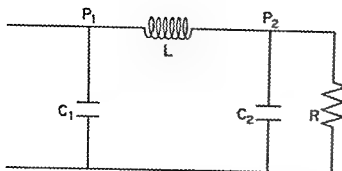


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The analysis program utilized the portion of the pressure curve occurring after closure of the aortic valve which is interpreted as the transient response of the arterial system to the pressure change occurring in systole. This pressure signal was measured at the femoral artery which was considered as point P_2 in Fig 1. The second heart sound (S_2) was used as a reference in determining the starting point for this transient. Watt and Burrus began their analysis at S_2 . This however does not take into account pulse wave velocity which must be considered in femoral recordings from dogs, particularly when vasodilators are given. During these drug infusions we have observed S_2 occurring before the systolic peak in the femoral artery. A diastolic notch remnant on the descending systolic wave was not always visible to serve as a starting point. Consequently

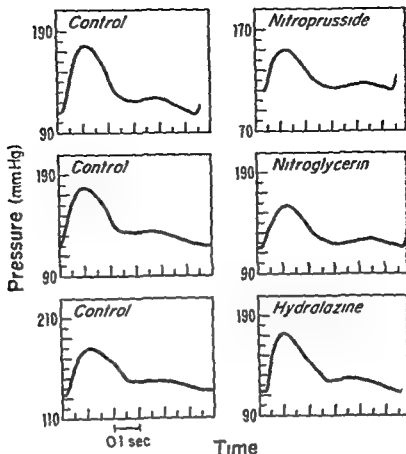


Fig 2 The effect of vasodilators on the arterial pressure pulse contour. An example from one of the dog experiments reported in this paper is shown.

the time from the end of S_2 to the systolic upstroke was taken as pulse wave transit time. Variations in presystolic ejection time have been considered negligible in comparison to transit time. This transit time was added to the S_2 time to determine the start of pulse wave sampling.

Fitting curves. An iterative curve fitting technique using a Gauss Newton algorithm was applied (Burrus personal communication). There are six variables in Equation 1 for which initial guesses are entered. At each iteration the algorithm moves each variable in a direction which reduces the differences between the calculated pressure (from Equation 1) and the actual pressure as measured.

Poor starting guesses for the six variables cause the iteration procedures to diverge. If the change in each parameter is limited to a part of the calculated correction the effect of poor initial guesses can be reduced. In practice step size was limited until the average error was near 3 mm Hg per point. The step size limitation was subsequently removed and the program converged to a

minimum value in 2 to 3 additional iterations.

In a few instances when the diastolic wave was broad the upstroke of the next beat occurred before the pressure at the end point of diastole fell below the pressure minimum between the systolic and diastolic waves. In these cases the program would not converge unless the pressure curve was extrapolated so that end diastole was below this minimum. The original curves were then fit satisfactorily using the parameters from the extrapolated curves as initial guesses. This problem occurred occasionally at high doses of NP and NTG.

Once the parameters have been determined it is possible to calculate the time constants RC_1 , L/R and RC_2 . Peripheral resistance (R) is determined as the ratio of mean arterial pressure to cardiac output. Central venous pressure was considered negligible in this calculation. Model parameters C_1 , C_2 , and L can then be calculated from the time constants and R . Impedance can be calculated using standard circuit methods.

fits obtainable with Equation 1 indicate that a third-order system can describe the major part of the transient diastolic decay observed in the pressure pulse. The transient decay will be determined by characteristics of vessels both proximal and distal to the point of measurement and will depend considerably on the summation of wave reflections in the region of measurement. Watt and Burrus² found that model components determined from data collected at several different sites along the arterial tree were very similar. However, it is yet to be determined whether changes in the pulse wave induced by vasodilating drugs are similar at different sampling sites in the arterial tree. The model is not meant to be an anatomical model but rather a device to interpret the gross mechanical behavior manifest in pressure measurements.

Site of measurement is of consequence in terms of its being proximal or distal. Proximal pressure measurements in man or the dog do not exhibit as prominent a diastolic wave as do distal recordings.¹¹ Bourgeois and associates¹ in fact interpreted the diastolic pressure decay in the thoracic aorta of the dog as a first order system and found its time constant to be proportional to peripheral resistance. This could be observed in a Windkessel model with a constant compliance. In general, curves can be fit to Equation 1 with greater accuracy if the measurement is distal because a diastolic wave is more prominent.

Several papers discussed below use frequency domain analysis to evaluate nonresistive components of impedance. The use of Fourier analysis to arrive at impedance values as a function of frequency requires few initial assumptions; the interpretations of the impedance curves must be based on a particular model. Taylor¹² proposed a nonuniform transmission line and then a more elegant model with seventh order branching and nonuniform elasticity. In this latter model there is little wave reflection at high frequencies. The impedance obtained experimentally at higher frequencies has therefore been interpreted as being representative of the characteristic impedance of the arterial system, which depends on its mechanical and geometrical properties. The frequency range in which impedance moduli are averaged to obtain a value for characteristic impedance is variable among investigators.

Propranolol was given in this study to limit reflex heart rate changes. Propranolol does not

significantly alter the effects of NP, hydralazine,¹³ or the vasodilatation due to NTG. Adams and colleagues¹⁴ measured characteristic impedance in dogs given NP and propranolol, although the frequency range they used for this calculation was questionable. They did not comment and it was not clear from their results whether propranolol changed the effect of NP; this value W_m are not aware of studies involving the interaction of propranolol and either NTG or hydralazine with regard to their effects on impedance. In the current study, propranolol did not completely prevent tachycardia in response to the vasodilating agents. This phenomenon has been previously observed.^{15,16}

The changes in the L parameters caused by the vasodilators indicate the manner in which they change the pulse contour. The significance of these changes may be interpreted using the electrical analog model L (inertance) is determined by properties of blood and the geometry of the vessels and in this case represents effective lumped inertance of a complex geometry. Since changes in vessel length and mechanical properties of blood are probably negligible in the present situation, a change in L may be assumed to be due to a change in effective mean vascular radius.

NTG caused an increase in L , thus suggesting a reduced vascular radius. The dominant vascular action of NTG is on the venous bed resulting in decreased venous return to the heart and a fall in cardiac output. Since peripheral resistance did not change in the present studies, the arterial pressure drop was due to the decreased cardiac output. This fall in distending pressure would be expected to passively decrease effective radius and increase L . Furthermore, Nicolosi and Papper¹⁷ found that the diameter of the aorta at any given pressure was decreased if venous return was decreased. This response could be abolished with alpha blockade or spinal cord transection. The reflex sympathetic discharge could be an additional factor in explaining the increase in L noted after NTG. Since L is proportional to the inverse of the radius squared, a small change in radius could considerably alter L .

The effect of hydralazine is confined to the arterial vascular bed. The fall in distending pressure after administration of the drug was due to a decrease in peripheral resistance. Inertance was not changed after hydralazine, perhaps

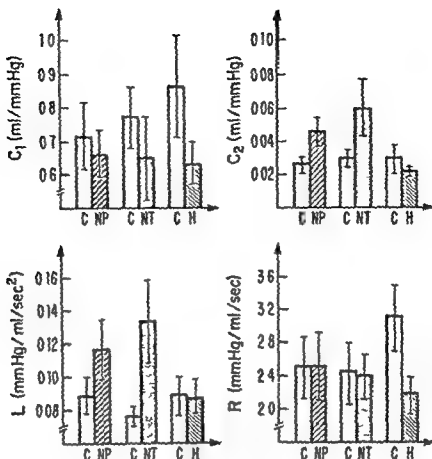


Fig 3 Variation of circuit parameters for modified Windkessel representation. Data taken from summary in Table I showing mean \pm standard error.

frequency domain studies. Clearly one cannot expect to reproduce impedance functions found from Fourier analysis of pressure and flow signals using a simple lumped parameter model. Impedance moduli determined from our results decreased monotonically with frequency. The reason this occurs in this third order system is explained by Watt and Burrus. The impedance moduli followed the same general patterns for peripheral vascular impedance at the low end of the frequency scale as those discussed in the literature.

Cardiac output fell after NP and NTG while it rose with hydralazine. Modest changes in heart rate occurred despite the use of propranolol.

Discussion

The purpose of this study was to investigate the effect of vasodilator drugs using a simple vascular model whose components are found from pulse contour analysis and knowledge of cardiac output. A stimulus for the study was the observation of pulse contour changes in humans given vasodi-

Table II The number of dogs which had the indicated change in model components following drug intervention

| Component changes | Nitroprusside study | Nitroglycerin study | Hydralazine study |
|-------------------|---------------------|---------------------|-------------------|
| Increased C_1 | 4/8 | 4/8 | 1/7 |
| Increased C_2 | 8/8 | 8/8 | 4/7 |
| Increased L | 5/8 | 8/8 | 2/7 |
| Decreased R | 5/8 | 6/8 | 7/7 |

C_1 = proximal compliance C_2 = distal compliance L = inductance
 R = peripheral resistance

lators for heart failure and the question of whether pulse contour analysis might be helpful in evaluating clinical response to this therapy. The canine vascular system is not meant to be a model of that system in human heart failure but rather is an experimental tool to determine whether descriptions of the actions of these drugs are consistent with their known effects.

Before discussing the results a few remarks should be made about this model. The good curve

arterial vasculature was used as a guide in interpreting the observed contour changes. The pressure curve during diastole has been viewed as the transient response of the arterial system and can be fit accurately to the equation

$$P(t) = a_1 \exp(-a_2 t) + a_1 \exp(-a_3 t) \cos(a_4 t + a_5)$$

The parameters in this equation and peripheral resistance were used to define the components of the third order Windkessel model consisting of proximal (C_1) and distal (C_2) compliances, an inertance term (L) and peripheral resistance (R). This model describes the gross mechanical behavior seen in the arterial system during diastole. The arterial pressure pulse, mean pressure and cardiac output responses to intravenous administration of sodium nitroprusside (NP), nitroglycerin (NTG) and hydralazine (H) were studied using computerized parameter estimating techniques to determine the parameters in the pressure equation and their relationship to the Windkessel components. All three drugs caused C to decrease but not significantly. NTG increased inertance from 0.076 to 0.134 mm Hg/ml/sec with a p value < 0.05 . NP increased C from 0.027 to 0.046 ml/mm Hg ($p < 0.01$). NTG also increased C from 0.030 to 0.060 ml/mm Hg ($p < 0.05$). Hydralazine had no significant effect on C but it did reduce R from 3.10 to 2.16 mm Hg/ml/sec ($p < 0.01$). Neither NP nor NTG showed a significant decrease in R . Thus the three vasodilators apparently have different vascular effects as demonstrated by the pulse contour analysis. Such an analysis may be a useful way to evaluate vasodilator therapy.

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part because it might directly dilate some of the vessels that influence L . Indeed the drug has been found to localize in the walls of muscular arteries.²¹ Proximally where more elastic tissue is present radius may be decreased because of less distending pressure and a balance of these effects could lead to a constant L . NP has effects on both venous and arterial vessels and we observed a nonsignificant increase in L that would be consistent with a summation of the above effects.

Significant changes in proximal arterial compliance were not observed with any of the drugs. According to Bergel's data on the static and dynamic viscoelastic properties of arteries particularly proximal arteries compliance should increase when pressure is reduced. In man Nichols and co-workers found differences in ascending aortic characteristic impedance between two groups of patients with coronary artery disease who had different blood pressures. The group with higher pressure had higher characteristic impedance. In the dog however O'Rourke and Taylor¹⁹ did not observe an increase in aortic characteristic impedance when they gave norepinephrine. Cox found that in the dog characteristic impedance in the thoracic and abdominal aorta brachial subclavian carotid and femoral arteries was independent of mean pressure in the range of 80 to 150 mm Hg. Cox and Bagshaw perfused the carotid sinus independently and found that ascending aortic characteristic impedance increased when carotid sinus pressure was either increased or decreased from a normalized value while characteristic impedance in several regional beds varied inversely with changes in carotid sinus perfusion pressure. Since characteristic impedance is determined by both compliance and inertance a decrease in pressure may have opposite effects on these separate parameters and could therefore result in a variable change in characteristic impedance. In our model impedance is largely determined by proximal compliance. It seems likely that arterial compliance is the result of various factors superimposed on inherent elasticity and at least in the dog it does not appear that changes in pressure have a dominant effect on compliance.

The effect of NP on characteristic impedance in dogs has been studied by Adams and associates and by Bagshaw and colleagues. The calculation of this quantity by Adams and associates may be questionable since it included some low frequen-

cies. Both studies found that characteristic impedance increased in the aorta during NP infusion. In the model used here the impedance seen by the heart at frequencies greater than zero is largely determined by proximal compliance since it is in parallel with a much larger impedance. This proximal compliance showed an average but non-significant decrease with NP. This decrease in C resulted in an increase in the impedance moduli calculated from our model in any frequency range above zero. Therefore these results using analysis of the pulse wave contour are compatible with previous studies using Fourier analysis of pressure and flow. We are not aware of any similar studies carried out using NTG or hydralazine with which to compare our results.

In the distal circulation we found that the actions of NP and NTG are different from those of hydralazine. NP has been observed to decrease characteristic impedance in regional beds; an effect which is consistent with the increase in distal compliance in our studies. We did not observe a change in peripheral resistance after NP a response that is not unexpected in the normal circulation.

Our results imply that NP and NTG reduce distal vessel stiffness whereas hydralazine increases distal vessel diameter without changing stiffness. We do not have enough information to determine whether these results are due to direct drug actions or are a result of reflex effects on the vascular system or are due to a combination of these effects.

In human heart failure the arterial system is in a constricted state. This constriction puts a further load on the heart and may lead to a further decrease in cardiac output. Vasodilators interrupt this cycle. It may be helpful when evaluating patients for this therapy to have information about impedance in addition to the other data usually obtained. The technique used in this study is a possible approach to obtain this information. Thus the form of the diastolic wave may provide clinically useful information on the state of the vascular bed. A study to examine vascular parameters in patients with heart failure before and after NP is currently under way.

Summary

The effects of three vasodilators on the shape of the arterial pressure contour in the dog were investigated. A modified Windkessel model of the

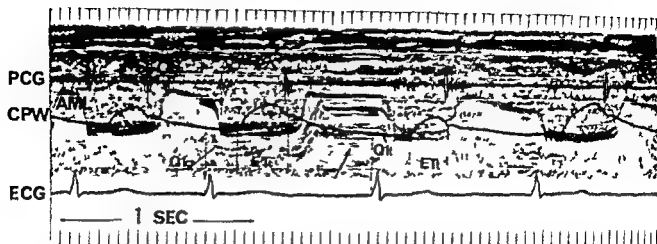


Fig 1 The echocardiogram of the mitral valve with simultaneous electrocardiogram (ECG) phonocardiogram (PCG) and carotid pulse wave (CPW) at a paper speed of 100 mm/sec. The diastolic descent rate of the anterior mitral leaflet is abnormally low (30 mm/sec). The tumor echoes are seen (arrow) in the second cardiac cycle behind the mitral cusp and disappear quickly at the beginning of ventricular systole. An opening snap (OS) is noted as the anterior mitral leaflet (AML) reaches its maximal anterior excursion. The preceding R-R interval of the second beat is 710 msec. QI interval (QIc) and ejection time (ETc) are 80 msec and 275 msec respectively. The third beat has a much longer preceding R-R interval (880 msec). However, because of the mitral orifice obstruction by the tumor, disproportionate prolongation of the QI interval (QIt = 120 msec) and shortening of the ejection time (ETt = 200 msec) are noted. S = first heart sound, S = second heart sound.

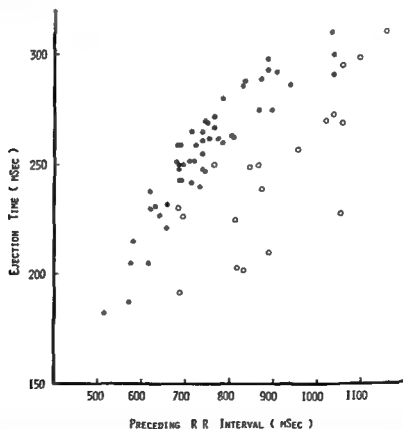


Fig 2 The relation between the preceding R-R interval and ejection time. Closed circles represent the ejection time with no preceding tumor echoes in the valve orifice. Open circles represent the ejection time just after the appearance of the tumor echoes. A logarithmic correlation ($y = -0.871 + 0.170 \ln x$, $r = 0.91$, $n = 59$) is found between the preceding R-R interval and the ejection time with no preceding tumor echoes. Significant reduction of the ejection time is seen after the appearance of tumor echoes in the valve orifice.

Case reports

Left atrial ball thrombus diagnosed by two dimensional echocardiography

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Left atrial ball thrombus is a rare disorder. The diagnosis of this serious yet curable lesion has been known to be difficult without cardiac catheterization and angiocardiography.¹ Although M mode echocardiography has proven useful in diagnosing left atrial tumors, detection of a ball thrombus in the left atrium is difficult by the conventional technique because of unpredictable motion of the thrombus. Two dimensional echocardiography allows continuous observation of moving structures with good anatomical orientation in selected cross sections. We report a case of left atrial ball thrombus diagnosed by two dimensional echocardiography and also describe some of the phonocardiographic and hemodynamic features.

Patient summary

A 55 year old woman was admitted in January, 1976 with a history of recurrent systemic embolization since 1968. She was found to have had a heart murmur in her mid thirties but was asymptomatic until August 1968 when she had an episode of cerebral emboli followed by fatigue and mild dyspnea on exertion. From 1968 to this

admission she had at least eight episodes of arterial embolization.

On admission physical examination revealed a heart rate of 65/minute at times irregular, blood pressure of 140/80 mm Hg and respiratory rate of 14/minute. The peripheral pulse in her left leg was diminished. The apical impulse was located in the fifth intercostal space at the midclavicular line and a right ventricular lift was felt at the left sternal border. The first heart sound was accentuated and the second sound was split normally with accentuation of the pulmonic component. An opening snap was present and was followed by rumbling diastolic murmur over the apex. No significant changes in auscultatory findings occurred with alteration of the patient position. The chest was clear to auscultation.

The electrocardiogram revealed atrial fibrillation with mild right ventricular hypertrophy. Chest x ray examination demonstrated an enlarged left atrium and dilated pulmonary outflow tract with some evidence of pulmonary vascular congestion. The hematocrit was 34.8% and hemoglobin was 11.2 g/100 ml. The erythrocyte sedimentation rate was increased to 89 mm in one hour. The total plasma protein was normal. Protein electrophoresis showed a slight increase in gamma globulin.

Simultaneous recording of the M mode echocardiogram with phonocardiogram, carotid pulse wave and electrocardiogram were performed (Fig. 1). The M mode echocardiogram revealed a reduced early diastolic descent rate of the anterior mitral leaflet with an increased left atrial

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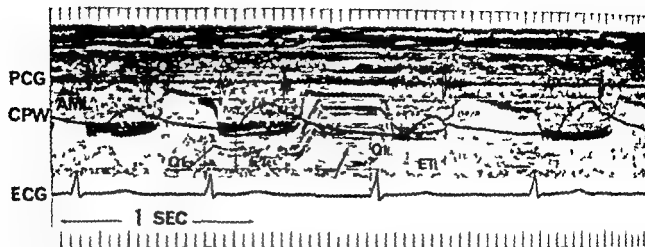


Fig 1 The echocardiogram of the mitral valve with simultaneous electrocardiogram (ECG) phonocardiogram (PCG) and carotid pulse wave (CPW) at a paper speed of 100 mm/sec. The diastolic descent rate of the anterior mitral leaflet is abnormally low (30 mm/sec). The tumor echoes are seen (arrow) in the second cardiac cycle behind the mitral cusp and disappear quickly at the beginning of ventricular systole. An opening snap (OS) is noted as the anterior mitral leaflet (AML) reaches its maximal anterior excursion. The preceding R-R interval of the second beat is 710 msec. Q-T interval (QT) and ejection time (ET) are 80 msec and 275 msec, respectively. The third beat has a much longer preceding R-R interval (880 msec). However, because of the mitral orifice obstruction by the tumor, disproportionate prolongation of the Q-T interval (QT = 120 msec) and shortening of the ejection time (ET = 200 msec) are noted. S = first heart sound, S = second heart sound.

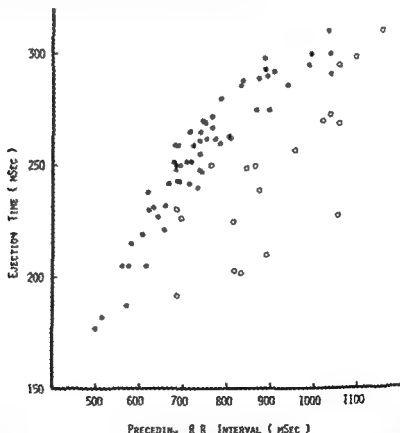


Fig 2 The relationship between the preceding R-R interval and ejection time. Closed circles represent the ejection time with no preceding tumor echoes in the valve orifice. Open circles represent the ejection time just after the appearance of the tumor echoes. A logarithmic correlation ($y = -0.871 + 0.170 \ln x$, $r = 0.94$, $n = 58$) is found between the preceding R-R interval and the ejection time with no preceding tumor echoes. Significant reduction of the ejection time is observed after the appearance of tumor echoes in the valve orifice.

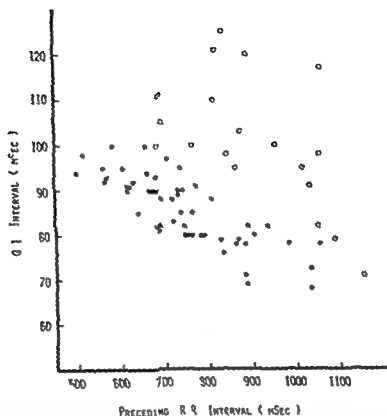


Fig 3 The relation between the preceding R R interval and Q to the first sound interval. Closed circles represent the Q to the first sound interval with no preceding tumor echoes. Open circles represent the Q to the first sound interval after the appearance of tumor echoes. Significant negative correlation ($y = 122 - 0.049x$ $r = 0.80$ $n = 58$) is seen between R R interval and the Q to the first sound interval with no preceding tumor echoes. The Q to the first sound interval is significantly prolonged after the appearance of the tumor echoes in the valve orifice.

dimension. It also demonstrated tumor echoes (arrow) appearing quite sporadically behind the anterior mitral leaflet during diastole and disappearing quickly at the beginning of systole. The diastolic descent rate of the mitral valve dropped suddenly from 30 mm/sec to almost zero with the appearance of the tumor echoes in the mitral orifice. The phonocardiogram confirmed the presence of the opening snap coincident with the E point of the anterior mitral leaflet. An early diastolic plop resulting from abrupt tumor movement¹⁸ was not identified in the beat with tumor echoes. A logarithmic correlation was found between the ejection time and the preceding R R interval and Q to the first sound interval was inversely proportional to the preceding R R interval. However, as can be seen there is a disproportional shortening of the ejection time and a prolongation of Q to the first sound interval in the beat following the appearance of the tumor echoes. These findings are summarized in Figs 2 and 3. The apexcardiogram did not show an early

systolic notch that was frequently observed in the case of left atrial myxoma.^{11,13}

The two dimensional echocardiogram was obtained along the long axis of the heart using Aloka SSD 200 (Aloka Co Ltd Japan). Recordings were made with a hand held 60 element 2.25 MHz transducer which provide 200 scanning lines in each cross section at frame rates between 40 to 100/second. The effective frame width was 5 cm. The multi crystal echocardiography demonstrated (Figs 4 and 5) reduced motion of the mitral cusps and the enlarged left atrium with the essentially normal aortic root and aortic valve leaflets. There was a highly mobile spherical tumor in the left atrium without a pedicle attached to the atrial wall. The tumor occasionally obstructed the mitral orifice immediately after the opening of the valve and moved back quickly out of the valve orifice into the left atrial cavity at the beginning of ventricular systole.

Cardiac catheterization revealed an elevated mean pulmonary capillary pressure of 21 mm Hg

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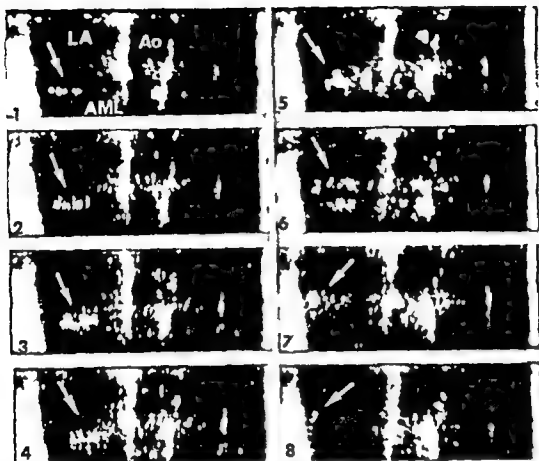


Fig 1 Selected frames (5 cm \times 12 cm) from the ultrasonic cross sections obtained along the long axis of the heart (1) (2) Highly mobile peripheral tumor (arrow) is seen in the left atrium (LA) measuring 2 cm in diameter. There is no pedicle attached to the thrombus. The motion of mitral valve is decreased and the LA was enlarged (3) (4) The tumor is approaching the mitral valve orifice (5) The tumor is obstructing the valve orifice during diastole (6) (7) (8) The tumor moves back quickly to the LA at the beginning of the ventricular systole. AML = anterior mitral leaflet. Ao = aorta.

beat following the appearance of the tumor in the mitral orifice the sudden shortening of the ejection time and the prolongation of Q to the first sound interval were noted. Both of these findings are indirect evidence of decreased left ventricular filling associated with an elevated left atrial pressure resulting from the sudden mitral orifice obstruction by the tumor. Detailed analysis of the data obtained by the conventional noninvasive techniques could provide critical clues for the diagnosis of the occlusive left atrial tumor.

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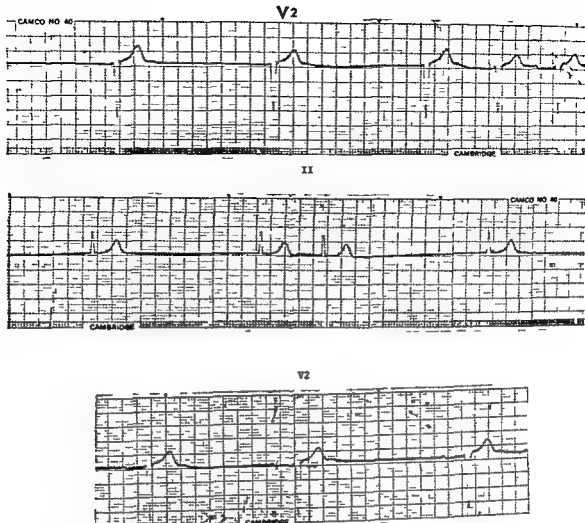


Fig 1B Short rhythm strips from preoperative ECG show junctional rhythm with variable antegrade block occasional sinus capture beats, and a period of profound sinus bradycardia with first-degree AV block

Case report

A 56-year-old white male physician who claimed to be in excellent health his entire life was evaluated medically prior to dental surgery in early January 1978. He denied any cardiac symptoms or signs. Physical examination was normal except for a pulse of 48 beats per minute. The patient is a highly trained athlete who for many years has played competitive tennis and has been an avid long-distance runner and cross-country skier. His preoperative electrocardiogram (Fig 1) revealed marked sinus bradycardia with a range of 30 to 50 beats per minute. An attempt was made to increase the patient's heart rate by vigorous exercise; however, it rose to only 64 beats per minute. A therapeutic trial of atropine 1 mg intravenously increased his heart rate to only 60 beats per minute. The patient underwent 24 hours of Holter electrocardiographic recording and was found to have periods of profound sinus bradycardia as low as 15 beats per minute when asleep as well as occasional sinus pauses and intermittent episodes of junctional rhythm (Figs 2 and 3). These arrhythmias were felt to be indicative of sick sinus syndrome. Although the patient steadfastly denied any symptoms or signs referable to bradycardia, it was decided to place a temporary and then permanent transvenous pacemaker.

The patient was readmitted to the hospital and monitored

overnight during which time his heart rate fell to 11 beats per minute without apparent symptoms (Fig 4). A temporary transvenous pacemaker was inserted via the right femoral vein without difficulty. When the tip of the pacing wire reached the right atrium, the patient developed asystole lasting approximately 30 seconds. A sharp precordial thump restored normal sinus rhythm. The pacing wire was then easily advanced across the tricuspid valve and into the apex of the right ventricle without further difficulty. Later in the day a permanent pacemaker was installed.

Following insertion of the pacemaker, the patient noted that he was now more awake and alert during sedentary activities. He then admitted that prior to pacemaker insertion he had been lethargic during periods of rest and inactivity and alert only during active exercise.

Discussion

The vast majority of ambulatory active persons with marked sinus bradycardia have typical symptoms of syncope or other obvious evidence of cerebral dysfunction.¹ The unique feature of this case is the totally unexpected finding of severe sinus node dysfunction and marked bradycardia.

Unusual manifestations of severe sick sinus syndrome

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The presence of marked sinus bradycardia is usually indicated by symptoms such as dizziness

or syncope particularly in active persons. Occasionally inactive elderly patients who are asymptomatic are found to have significant sinus node dysfunction with bradycardia on routine electrocardiogram. This paper presents a case of an extremely athletic middle aged man who was found to have severe sinus node dysfunction with profound sinus bradycardia and prolonged sinus pauses in the apparent absence of symptoms

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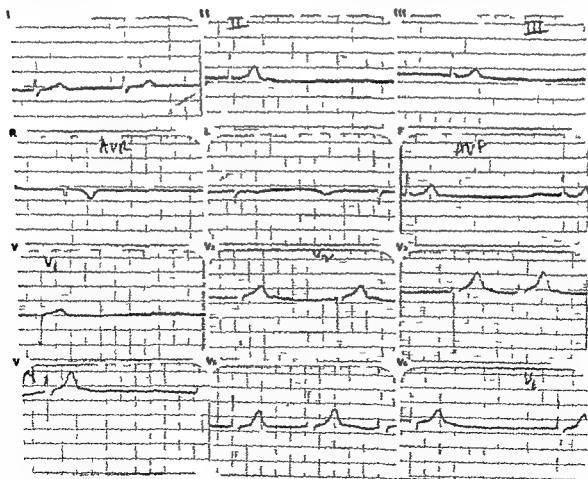


Fig 1A Preoperative electrocardiogram showing junctional rhythm with variable exit block.

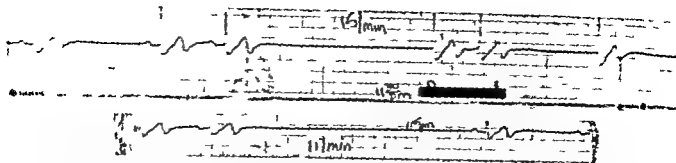


Fig 4 Telemetry strips obtained while the patient was in bed attempting to read a book. Top strip shows sinus bradycardia premature atrial beats with capture and sinus arrest terminated by junctional escape beats. Bottom strip shows 5 1/2 seconds sinus pause

in a highly trained athlete who denied subtle symptoms until his cardiac function was improved with a pacemaker. It appears that he may have been exercising excessively to remain awake and alert through altered autonomic tone. We feel, therefore, that there is a subgroup of patients with sick sinus syndrome who do not have the typical cerebral symptoms but may rather express a feeling of well being only during active exercise. When such symptoms are exhibited we suggest that the patient have ambulatory 24 hour cardiac monitoring in order to demonstrate possible sinus node dysfunction or other bradyarrhythmias.

Another important feature of this case was the episode of prolonged sinus arrest occurring when the temporary pacemaker tip reached the right atrium. The exact electrophysiological mechanism is unclear; however, the episode might have been prevented had the patient been given atropine prior to the temporary pacemaker insertion. Therefore, perhaps patients with severe sick sinus syndrome manifested by markedly prolonged sinus pauses in the range of 4 to 5 seconds should be given a substantial dose of atropine (10 to 20 ml intravenously) shortly before the insertion of a temporary pacing wire in order to avert prolonged sinus arrest.

Summary

An extremely athletic 56-year old male physician was found to have profound sinus bradycardia. His only symptom was markedly increased alertness while actively exercising. During pacemaker insertion he had an episode of prolonged sinus arrest terminated by a precordial thump. This case suggests that exercise can alter autonomic tone and increase cardiac output in sick sinus syndrome causing improvement in possibly unrecognized subtle cerebral symptoms. It also appears that patients with profound sinus bradycardia should be given a substantial dose of atropine prior to pacemaker insertion in an effort to prevent prolonged sinus arrest.

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Unusual manifestations of sinus bradycardia

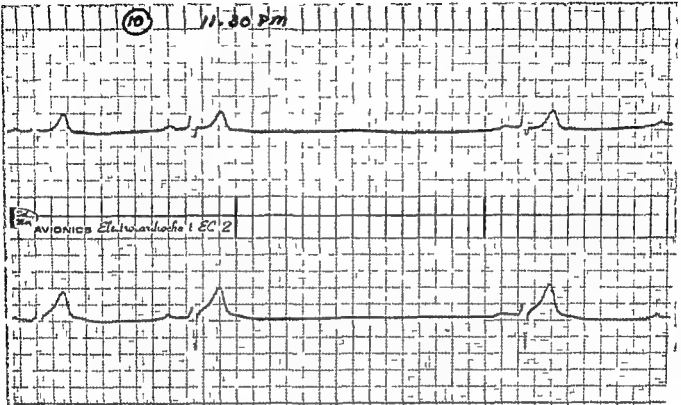


Fig 2 Holter recording shows 4 second sinus pause and first degree atrioventricular block

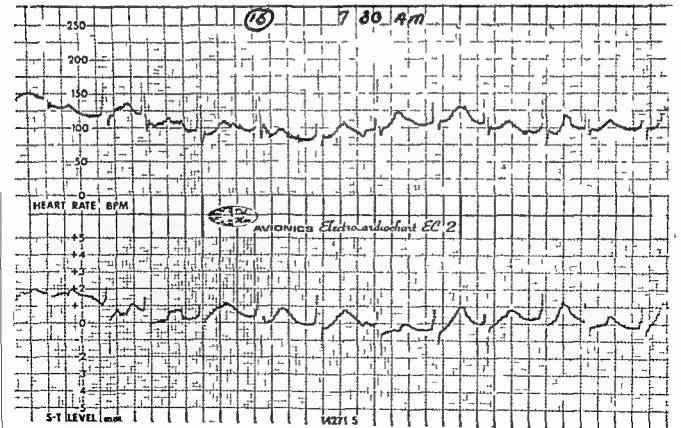


Fig 3 Holter recording during jogging shows accelerated junctional rhythm with occasional atrial capture beats

Table I Initial symptom in 60 patients with giant cell arteritis*

| Symptom | Number of patients |
|------------------------|--------------------|
| Polymyalgia rheumatica | 24 |
| Headache | 18 |
| Malaise | 5 |
| Fever | 4 |
| Jaw claudication | 3 |
| Scalp nodules | 2 |
| Visual loss | 2 |
| Aortic arch syndrome | 1 |
| Confusion | 1 |
| Total | 60 |

*Modified from Reference 6

Table II Clinical findings in 60 patients with giant cell arteritis*

| Finding | Group |
|--|------------|
| Sex | |
| Male No | 12 |
| Female No | 48 |
| Age at onset, yr† | 69 (51-83) |
| Duration of disease before treatment months† | 6 (½-24) |
| With polymyalgia rheumatica No | 31 |
| Symptoms related to | |
| Arteries No | 52 |
| Headache No | 31 |
| Jaw claudication No | 22 |
| Scalp tenderness No | 13 |
| Calf claudication No | 4 |
| Arm claudication No | 2 |
| Swallowing claudication No | 1 |
| Tongue claudication No | 1 |
| Disturbance of vision No | 15 |
| Permanent loss of vision No | 3 |
| Abnormal arteries on examination No | 40 |

*Modified from Reference 6

†Shown as mean with range in parentheses

malaise fatigue or weight loss. Fatigue occurs in nearly all patients and the majority report anorexia and weight loss.³ Constitutional manifestations occasionally are the only findings present and may be attributed by those around the patient to aging or senility. Such cases serve as reminders of the need to consider giant cell arteritis in older individuals with failing health. Psychosis, mental depression, and confusion may occur also. A low grade fever is frequent and occasionally patients may present as a case of fever of unknown origin.

Because of the prominence of these nonspecific symptoms, patients sometimes undergo extensive evaluations including exploratory laparotomy to rule out occult malignancy or infection before the presence of giant cell arteritis is realized.

Headache is a common initial symptom and is present in up to 90% of patients in some series. The headache typically is severe and is localized to the region of the temporal arteries.¹⁻³ The pain may be constant or intermittent and may be described as boring or lancinating in character. However, there is such variation in the location and type of pain that giant cell arteritis should be considered in any older patient with a new headache. When scalp pain is also present, the patient may complain of discomfort combing the hair, wearing a hat, or laying the head on a pillow.¹⁻³

Temporal artery abnormalities are the most helpful physical findings in recognizing giant cell arteritis and are detectable in the majority of patients.³⁻⁶ The combination of a tender, arthritic, swollen or nodular temporal artery in association with other symptoms of arteritis virtually assures the diagnosis (Fig. 1). The patient may give a history of recent tender nodules or swelling in the area of the temporal vessels which have resolved by the time the physician is consulted. The absence of a pulse in a temporal artery is highly suggestive of arteritis, but a subjective difference in the strength of the pulsation between the two sides is generally not a reliable indication of disease.

Jaw claudication was felt by Horton³ to be pathognomonic of temporal arteritis and was associated with involvement of the facial artery. It occurs in up to one half to two thirds of patients, but its presence may be overlooked if the patient is not specifically questioned about pain or fatigue in the jaw muscles with chewing. It must be differentiated from the pain in the temporomandibular joints that develops with single opening or closing of the mandible. A similar type of claudication less commonly occurs in the tongue with chewing or in the muscles of deglutition with repeated swallowing.³

Polymyalgia rheumatica is defined as aches and stiffness in the neck, shoulder girdle and/or hip girdle associated with an elevated erythrocyte sedimentation rate.¹⁴⁻²⁵ The pain most commonly is felt in the neck and shoulder girdle but may also be severe in the hip girdle muscle.

Review

Giant cell (cranial) arteritis ■ clinical review

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Giant cell arteritis is a disease of the elderly which when recognized early in its course can be treated effectively with corticosteroids. Such treatment results in the relief of symptoms and prevention of blindness or other complications due to occlusion or rupture of involved arteries. The term giant cell arteritis has been criticized because giant cells are not found exclusively in this disease and in addition they may be difficult to identify in artery biopsy sections from some patients with typical symptoms. Cranial arteritis connotes the most frequent location of the arterial involvement but also has shortcomings because the arteries in the neck and proximal branches of the aortic arch may be affected as well as those of the head. Other designations which are used include temporal arteritis, granulomatous arteritis, polymyalgia arteritica and arteritis of the aged but all also have drawbacks to their usage. The first report of the disease was by Hutchinson in 1890¹ who hypothesized that his patient's head pain and inflamed artery was caused by a tight fitting hat. That explanation seems humorous today but we cannot yet claim any greater understanding of the etiology. The disease was not widely recognized until the classic report of Horton and colleagues in 1932 in which the biopsy findings first were described. Since then the clinical spectrum of giant cell arteritis has expanded so that

we now recognize its association with polymyalgia rheumatica and include it in the differential diagnosis of headache fever of unknown origin and large vessel arteritis.

Epidemiology

Giant cell arteritis is not a rare disorder. A recent investigation showed that the prevalence of giant cell arteritis in the population aged 50 years and older was similar to that of ankylosing spondylitis.² The average annual incidence per 100 000 population aged 50 and older rose from 5.1 in 1950 to 54 in 1970 to 74 probably due to greater recognition of the disease.³ The disease rarely occurs in persons under age 50 years and reaches its greatest incidence in those over age 70.³ In four large series totaling 197 patients 65% were in women.⁴⁻⁷ Giant cell arteritis has been reported mainly in persons of European ancestry but its occurrence in blacks has been noted in several recent case reports.⁸⁻¹⁰ These observations and several reported instances of familial aggregation suggest that genetic factors may influence its occurrence.^{3,7,11-13} There is no detectable association between giant cell arteritis and malignancy or other forms of vascular disease.³ Several reported cases have been associated with rheumatoid arthritis but thus far no etiologic association between the two diseases has been established.^{3,5,14}

Clinical findings

Tables I and II show the symptoms and findings in a series of 60 patients studied prospectively.⁶ The onset of the illness may be abrupt or insidious. A patient may note the rapid development of severe proximal myalgias or headache and swollen temporal arteries.⁶ But more often the disease begins insidiously with onset of nonspecific constitutional manifestations such as

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incidental findings in the older age group. Claudication of the upper or less often of the lower extremities and diminished peripheral pulses usually improve with corticosteroid treatment when due to giant cell arteritis. Gangrene of an extremity, ischemic neuropathies and Raynaud's phenomenon are less frequent. An unusually tender carotid or other large artery indicates involvement of that vessel.

Occlusions of large vessels are sometimes found in patients with widespread disease and in some instances aortic rupture and dissection occurs. Aortic valve insufficiency has been reported as a consequence of aortic dissection. Infarctions of the brain and myocardium due to giant cell arteritis have been demonstrated at autopsy in some cases. These complications however are unusual. A recent epidemiologic study showed no increase in occurrence of cardiac disease or stroke in patients with giant cell arteritis over that expected to occur in the general population. Involvement of renal arteries may be found at autopsy and erythrocyte casts may be present in the urine. Renal insufficiency or failure however is rare. Involvement of the aorta and other large vessels is probably much more common than can be detected clinically. In one study, medial necrosis of the aorta was found in all five patients with giant cell arteritis coming to autopsy and arteritis was found in 17% of 889 consecutive postmortem cases when sections of the temporal arteries and aorta were examined.

Other manifestations of giant cell arteritis which are uncommon but nevertheless of interest are glossitis, recurrent blanching of the tongue, gangrene of the tongue, and an altered sense of taste and smell. Scalp necrosis has been reported in a few cases but rarely, if ever occurs, as a result of temporal artery biopsy.

Laboratory findings

The erythrocyte sedimentation rate is the most helpful laboratory test in the evaluation of giant cell arteritis and is markedly elevated in virtually all patients. For practical purposes, the absence of a high erythrocyte sedimentation rate eliminates temporal arteritis from diagnostic consideration although giant cell arteritis has been documented by biopsy in a few patients with a normal or mildly elevated erythrocyte sedimentation

rate. A mild normochromic or hypochromic anemia is present in the majority of patients. The hemoglobin concentration is usually in the range of 10 to 12 g/dl but occasionally may be lower. The leukocyte count is usually normal but elevations in the range of 10 000 to 20 000 white cells per mm³ occur in about 40% of patients. The serum protein electrophoresis characteristically reveals an elevated alpha 2 globulin. Liver function tests including glutamic oxalacetic transaminase and alkaline phosphatase levels are elevated in many patients and revert to normal with corticosteroid therapy. Liver biopsies generally are normal or show only mild fatty changes but may show granulomatous hepatitis.

Temporal artery angiography has been used to establish the diagnosis or to identify abnormal segments of the vessel to biopsy. The procedure however is time consuming and may have little advantage over temporal artery biopsy alone. In some cases giant cell arteritis is first recognized by the typical angiographic findings in large vessels showing multiple stenotic areas and occlusions at the end of tapered arterial segments.

The relationship of giant cell arteritis to polymyalgia rheumatica

Whether all patients with polymyalgia rheumatica have the same underlying disease is controversial. Various investigators have found that from 24 to 78% of patients with polymyalgia rheumatica show histologic evidence of vasculitis if their temporal arteries are biopsied.

The close association between the two entities has led to speculation that all patients with polymyalgia rheumatica have giant cell arteritis. But this idea has not been universally accepted.

The majority of patients with positive biopsies have manifestations of giant cell arteritis other than polymyalgia rheumatica. The crux of the matter is what is the risk of serious vascular complications, particularly blindness, in patients with pure polymyalgia rheumatica. There is incomplete data to answer this question definitively, but the risk of blindness in these patients appears to be relatively small. Many if not most patients with only polymyalgia rheumatica can be satisfactorily treated with non-steroidal anti-inflammatory drugs or low doses of corticosteroids without ever developing

Characteristically the symptoms disturb sleep and there is an accentuation of soreness and stiffness in the morning. Although the patient often describes the discomfort in muscle areas local muscle tenderness is not usually as marked as the pain elicited by movement of the shoulders or hips.⁷⁻⁹ Other joints particularly the knees and sternoclavicular joints may be swollen.¹¹⁻¹³ Peripheral joint abnormalities when present however are usually mild and transient.¹¹⁻¹³ Polymyalgia rheumatica occurs in 50% or more of patients with giant cell arteritis and may be the initial manifestation or may appear for the first time as treatment with corticosteroids is being withdrawn.⁷ Muscle enzymes, electromyograms and muscle biopsies are normal.²¹ Careful histologic studies have demonstrated inflammatory changes in shoulder synovium, capsule, bursae and other periarthritic structures and joint scanning with technetium pertechnetate has shown increased uptake in the shoulders and other joints.³ These findings suggest that synovitis rather than arteritis or muscle disease is the source of the symptomatology in patients with polymyalgia rheumatica.

Visual manifestations are present in 25 to 50% of patients and reflect ischemia of the involved structures.^{3,6} Transient visual blurring is not uncommon but by itself may not strongly suggest giant cell arteritis. Diplopia occasionally accompanied by ptosis is felt to be secondary to involvement of arteries supplying ocular muscles or cranial nerves but this has not been well studied histologically.⁶ Partial or complete visual loss is usually permanent but may be preceded by transient blindness.^{1,2} The funduscopic picture of ischemic optic neuritis with pallor and swelling of the optic disc often accompanied by small hemorrhages and a few retinal cotton wool patches is seen in the majority of patients with blindness.¹ Autopsy studies have demonstrated involvement of the ophthalmic and posterior ciliary arteries in individuals with this ocular complication. Less commonly the picture of central retinal artery occlusion is observed and in a few patients central blindness due to infarction of the occipital cortex has been demonstrated.^{1,2,41}

Visual loss is usually associated with clinical abnormalities of the temporal arteries and typically begins abruptly in one eye and progresses over the next few days.²⁹ In individuals with



Fig. 1 Swelling of both branches of the left superficial temporal artery in a patient with giant cell arteritis. Enlargement of a temporal artery to this degree is uncommon. From Rodnan G P, Mannik M, Schumacher H R, Jr, eds. *Primer on the Rheumatic Diseases*, eighth edition. Atlanta: The Arthritis Foundation (In press). Reproduced with permission.

bilateral involvement impairment in the second eye is usually noted a few days or weeks after the initial eye symptoms.¹⁹ Blindness rarely develops either as an initial manifestation or after more than one year of disease.^{4,41} In one series of 122 patients visual loss was the initial symptom in only two individuals. When established the visual deficit rarely improves despite treatment with corticosteroids.⁴¹ Even the most encouraging review cited visual improvement with treatment in only 15% of patients.⁶

The frequency of blindness reported in patients with giant cell arteritis has decreased since the use of corticosteroids but this may be due at least in part to increased recognition of patients with milder forms of the disease.⁴² Less commonly reported ocular findings are periorbital edema, conjunctivitis and ophthalmomalacia.^{1,9} Visual hallucinations and bruits over the orbit may occur and may resolve with corticosteroid treatment.²⁹

Large artery involvement is clinically detectable in approximately 10% of patients.^{30,31} Bruits are commonly encountered but may be

disease.³ Some biopsies show only intimal proliferation and fragmentation of the internal elastic lamina. These milder changes have been termed "healed temporal arteritis" but may be the only histologic abnormality visible in biopsy specimens from some patients with active disease.^{2, 71} These latter abnormalities may be differentiated from the normal aging changes of temporal arteries which have been well described in normal and autopsy studies.^{72, 73}

The most important aspect of the histopathology for the clinician to remember is the occurrence of skip lesions. Isolated foci of arteritis have been well documented by serial sections of long segments of involved vessels in 28% of patients.⁷⁴ In some instances the temporal artery biopsy from one side is normal but the contralateral artery biopsy is positive. These findings emphasize the need to obtain a long segment of artery and to examine multiple histologic sections of the specimen. If a portion of the vessel is abnormal on clinical examination that segment of course should be biopsied initially. If frozen sections from one side are negative in a patient strongly suspected of having arteritis the contralateral temporal artery should be biopsied.

The relationship to other forms of vasculitis

There are no clear cut histopathologic differences between giant cell arteritis and Takayasu's disease and there is a considerable overlap in the clinical findings. These entities are separated predominantly on the basis of age and epidemiologic differences. Takayasu's disease typically occurs in young females and is an arteritis predominately involving large vessels. Giant cell arteritis occurs almost exclusively in persons over age 50 and involvement of extracranial large vessels is detected in only a minority of cases. Headache and polymyalgia rheumatica are more characteristic of giant cell arteritis and this disease appears to carry a more favorable prognosis. Takayasu's arteritis is less responsive to treatment and is sometimes associated with erythema nodosum and hypertension which are not features of giant cell arteritis. For these reasons it appears that these are separate entities but a few patients with otherwise typical giant cell arteritis develop large artery involvement and follow a clinical course indistinguishable from Takayasu's disease.^{2, 75}

Giant cell arteritis is more clearly separated from polyarteritis. Though these entities both occur in older individuals the clinical course, histopathology, and prognosis are sufficiently different to distinguish between them. It should be noted however, that patients with polyarteritis may occasionally have involvement of the temporal arteries.^{76, 77}

Giant cell granulomatous angitis of the central nervous system appears to be a separate entity with predominant involvement of the small leptomeningeal and intracerebral arteries and veins. The manifestations are severe neurologic changes and the illness is generally progressive and fatal.⁷⁸

Diagnosis and treatment

A temporal artery biopsy should be obtained in all patients suspected of having giant cell arteritis including those patients in whom the clinical diagnosis seems certain. Although the initial often dramatic improvement with corticosteroids seems to confirm the diagnosis, biopsy proof often becomes important later in the course when the clinical picture is blurred because the symptoms are suppressed but the sedimentation rate is above normal and the patient has suffered complications of therapy. This is especially true if the physician who is treating the patient is not the one who made the initial diagnosis. In these situations subsequent treatment decisions are facilitated if the diagnosis initially was confirmed histologically.

Corticosteroid therapy should be instituted when the diagnosis of giant cell arteritis is made. In patients in whom the clinical impression of giant cell arteritis is strong prednisone can be started immediately and a temporal artery biopsy can be obtained the following day. Small or moderate doses of corticosteroids (10 to 20 mg prednisone per day or equivalent) may alleviate the symptoms within a few days but larger doses are indicated initially to prevent blindness. The great majority of patients with giant cell arteritis who lose vision do so before treatment is initiated. This in itself speaks strongly for the efficacy of corticosteroids in preventing visual complications. The few patients who develop visual loss after starting corticosteroids have usually done so within a few days of starting high doses of corticosteroids or within a few weeks of

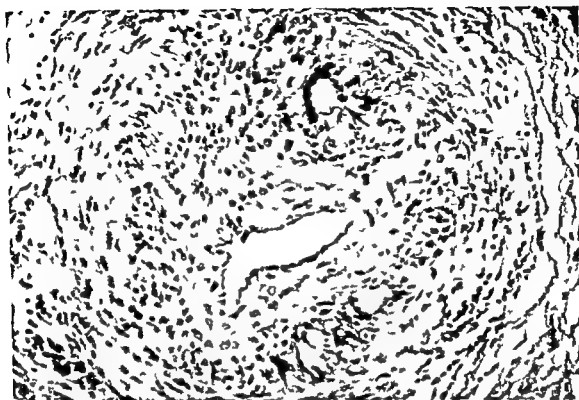


Fig 2 Giant cell arteritis in small branch of temporal artery. Multinucleated giant cells (one pointed out by the arrow) are present at junction of media and intima. There is extensive disruption of all layers of the vessel wall (Hematoxylin and eosin, original magnification $\times 400$). From Rodnan G I, Mannik M and Schumacher H R Jr, eds. *Primer on the Rheumatic Diseases*, eighth edition. Atlanta: The Arthritis Foundation (In press). Reproduced with permission.

vascular complications and with eventual resolution of symptoms. The presence of polymyalgia rheumatica alone therefore does not necessitate the use of high dose corticosteroid therapy with its attendant morbidity. When steroids are given, most patients experience marked relief of symptoms with 5 to 15 mg of prednisone or equivalent per day. Even with the use of these low doses of corticosteroids a favorable response is usually so predictable that some authors consider it helpful diagnostically. A similar degree of improvement in aching and stiffness may be seen, however, in patients with rheumatoid arthritis or systemic lupus erythematosus.

Whether a patient with polymyalgia rheumatica alone should have a temporal artery biopsy is a decision that needs to be individualized and may be influenced by the severity of the accompanying constitutional symptoms as well as the compliance, reliability, and general medical condition of the patient. The yield of positive temporal artery biopsies is low in patients who after a careful history and physical examination

have no other findings suggestive of temporal arteritis. Furthermore, a negative biopsy does not ensure that a patient will not later develop other manifestations of temporal arteritis. Patients treated for polymyalgia rheumatica without a biopsy and those with negative biopsies should be advised to notify their physician if a new head ache, jaw claudication, temporal artery swelling, or visual changes develop.

Pathology

The characteristic histologic findings of giant cell arteritis are a mononuclear cell inflammatory infiltrate throughout the vessel wall, disruption of the internal elastic lamina, and the presence of giant cells in the region of the internal elastic lamina (Fig 2). Intimal thickening and thrombosis are additional features. The round cell infiltrate in some biopsy specimens may be limited to portions of the wall near the internal elastic lamina. Giant cells are not detectable in some cases but their presence or absence does not substantially affect the clinical course of the

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starting treatment with doses equivalent to 5 to 20 mg prednisone per day.^{2,3,11,14} To minimize vascular occlusion or ruptures 40 to 60 mg of prednisone per day, or equivalent, is recommended for the first month. After that, if reversible symptoms have cleared and the tests are normal, the dose is gradually tapered using the patient's clinical course, the erythrocyte sedimentation rate, the alpha 2 globulins, and hemoglobin levels as guidelines. Most patients require lower doses (10 to 20 mg prednisone per day, or equivalent) of corticosteroids for several months.³ Patients with extensive large artery involvement may have a worse prognosis and sometimes require treatment with high dose corticosteroids for a longer period of time than one month. In one study over one half of patients required treatment for less than a year.³ Corticosteroids can be discontinued in most patients within two years, but a few patients require more prolonged treatment usually because of relapses or lingering symptoms such as headache or musculoskeletal pain which become severe when the corticosteroid dose is further reduced.³ Symptomatic relapses usually occur shortly after the corticosteroid dose is reduced or stopped altogether. After a patient has remained asymptomatic for one month or longer off corticosteroids, further relapses are infrequent.³ Rarely, however, patients on long term treatment have developed visual loss. This possibility makes it necessary to restart or increase the dose of corticosteroids as soon as a relapse is apparent.^{3,11,14} Alternate day corticosteroid treatment has been evaluated in a controlled study of giant cell arteritis and is not as effective as daily therapy. Persistent symptoms of polymyalgia rheumatica alone may be adequately controlled with aspirin or other non-steroidal anti-inflammatory drugs so that in many instances prednisone may be reduced further or stopped. Histologic evidence of giant cell arteritis may persist in arteries examined several years after the onset of disease but this does not appear to be an indication to continue therapy in the absence of clinical evidence of active disease.

Long term follow-up of unselected patients has shown that giant cell arteritis has no detectable effect on survivorship.³ This favorable prognosis it should be noted, is seen with patients who are treated and the survivorship of untreated

patients is unknown. It is clear that patients sometimes succumb to the complications of the disease, but not with a frequency that significantly affects overall survival.

Summary

Giant cell arteritis is a disease of the elderly which is more common than previously recognized. It is important to be aware of this condition because treatment effectively relieves symptoms and prevents serious complications. The disease is suggested when an elderly patient complains of constitutional symptoms, headache, jaw claudication, or the musculoskeletal manifestations of polymyalgia rheumatica. Abnormalities in temporal arteries or other cranial arteries, or evidence of large vessel involvement may be detected by physical examination. A markedly elevated sedimentation rate in association with other clinical features of the disease strongly suggests giant cell arteritis, but a biopsy should be performed to confirm the diagnosis. Corticosteroid therapy should be started promptly in high doses in order to prevent blindness. Prolonged treatment with lower dose corticosteroids is generally necessary for up to 1 to 2 years and sometimes longer for continued symptomatic relief. Long term follow-up of treated patients has demonstrated no detectable effect on survivorship.

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Difficult problems in the diagnosis of chest pain

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Chest pain is not only a common symptom but one which evokes considerable anxiety among patients and clinicians alike. In middle aged or older people, a new or recurrent pain in the chest or arm is apt to suggest coronary heart disease and the response of a concerned physician is likely to emphasize this possibility. As a general rule, however, while it is in the patient's best interest to err on the side of overdiagnosis of acute coronary heart disease, there is good reason not to do so with chronic chest pain syndromes. Failure to recognize acute coronary heart disease could result in a premature death which might have been prevented in an inpatient facility. However, the risk of sudden death from chronic stable coronary heart disease is relatively low. Moreover, it is not easily prevented and an erroneous diagnosis could easily evoke unnecessary anxiety and have adverse emotional, domestic, and financial consequences. Thus, a chronic chest pain syndrome, particularly one with atypical features for an ischemic origin, should always be met with appropriate skepticism with special attention given to those characteristics or findings which do not "fit" the pattern of typical angina pectoris. Although no physician wishes to be blamed for overlooking the diagnosis of chronic coronary heart disease, one of the more rewarding experiences in medical practice is to be able to replace the cloud of coronary disease with a less serious or sometimes quite benign alternative.

The differential diagnosis of coronary heart pain includes a wide variety of non-cardiac conditions: disease of the esophagus, lungs, gallblad-

der, osteoarthritis of the upper spine, bursitis of joints, disease of the muscles, tendons, or cartilage of the chest wall, etc. However, it is not sufficient merely to establish that the pain is or is not of cardiac origin, or even that it is ischemic heart pain. Indeed, the prognostic implications and frequently the therapy of ischemic heart pain may be substantially different in the patient with hypertrophic cardiomyopathy, angina pectoris with normal coronary arteries (Gorlin-Likoff syndrome), mitral valve prolapse, aortic stenosis, etc. *vis à vis* the patient whose ischemic pain is due to obstructive coronary artery disease. Although regional myocardial ischemia may be common to all of these, an accurate etiologic diagnosis is essential for proper management. In most instances, the mimics of coronary heart pain present special features which lead the clinician to question the diagnosis of angina pectoris (Table I). In order to take full advantage of these clues, a review of the characteristic features of angina pectoris due to coronary artery disease is essential.

Angina pectoris

It is generally believed that the basis for angina pectoris is relative myocardial ischemia. Although a specific nerve stimulant produced by ischemia has not yet been identified, it is likely that afferent sympathetic nerve endings are activated by a chemical product of ischemia. These afferent sympathetic nerves, found in the walls of the coronary vessels and in the myocardium, carry impulses to the cervical and upper thoracic sympathetic ganglia and then to the spinal cord via the dorsal roots of the first five thoracic segments.¹ Considering the potential variations in nerve traffic across this afferent network, the widely variable expression of ischemic heart pain syndromes is not at all unexpected.

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nary heart disease but not necessarily to those with acute coronary syndromes. Chest pain may last 15 to 20 minutes or more in patients with unstable angina and for hours in the case of frank myocardial infarction.

Factors which provoke pain. Angina pectoris is generally brought on by physical or emotional stress. frequently the combination of the two will provoke pain when either factor alone may not do so. Cold weather is a potent factor in evoking angina pectoris by virtue of reflex vasoconstriction of the coronary vessels and as a consequence of the pressor response to cold. Isometric hand grip too will provoke angina pectoris in a susceptible individual. Indeed the hypertensive and chronotropic response to handgrip probably accounts in large part for the familiar history of angina pectoris developing while a subject carries even a light suitcase at the airline terminal. Post prandial angina pectoris is common and occasionally presents as the sole manifestation of ischemic heart pain. While the mechanism has been poorly understood recent animal studies suggest that receptors located in the stomach may be responsible for a significant pressor and heart rate response to capsaicin administration. Post prandial angina pectoris should be distinguished from abdominal angina. While post prandial ischemic pain is the essence of both conditions in the latter ischemic bowel is the source of the pain.

According to Gorlin the reproducibility of angina pectoris is surprisingly low in most patients with coronary disease except in subjects with advanced three vessel disease or left main coronary artery obstruction. Certainly we are familiar with the first effort phenomenon in the individual who experiences angina pectoris on the first fairway of a golf course and then completes the course without pain thereafter. Similarly some patients with an unstable form of angina pectoris may develop symptoms with minimal or no provocation—and several weeks later engage in considerable physical exertion without pain with no detectable evidence of an infarction in the interim. One very helpful characteristic of angina pectoris is that it is extraordinary for a person suffering from ischemic pain to feel better in the recumbent position. The larger cardiac dimensions associated with recumbency increase myocardial oxygen requirements and thus aggravate angina pectoris.

Relief of pain. Angina pectoris due to coronary artery disease is generally relieved within 1 to 4 minutes by sublingual nitroglycerin. Relief following carotid sinus pressure is almost immediate and is dependent upon cardiac slowing. Relief of angina pectoris during the Valsalva maneuver occurs during the strain phase (phase 2) of the maneuver and is probably the consequence of a decrease in myocardial wall force (decrease in ventricular pressure and dimensions).*

The response of angina pectoris to sublingual nitroglycerin is extremely useful as a diagnostic therapeutic test. It should be remembered however that the response must be prompt that it occurs within five minutes and generally less than three minutes. Furthermore prompt relief of pain following sublingual nitroglycerin is not diagnostic of angina pectoris. Esophageal spasm may be relieved by nitroglycerin and the response to this medication of pain due to spasm of the sphincter of Oddi is often just as dramatic as that of angina pectoris.

Physical examination. In the absence of congestive heart failure the physical examination is generally not very helpful in confirming the presence of coronary heart disease but it is a crucial procedure in detecting many of the syndromes which masquerade as coronary disease. Diastolic filling sounds (S_1 or S_1) are present in less than half of patients with chronic coronary heart disease² and thus this finding is of little help in establishing the diagnosis. A systolic bulge at or near the apex may be found on palpation and occasionally paradoxical splitting of the a_2 will be detected. On the other hand a careful cardiac examination during an episode of ischemic heart pain may prove most rewarding. A systolic bulge diastolic filling sound paradoxically split S_1 or mitral regurgitant murmur which disappears when the pain subsides is virtually pathognomonic of ischemic heart disease. Physical findings suggestive of an underlying metabolic abnormality predisposing to premature atherosclerosis such as skin or tendon xanthomas, hypertension, diabetic retinopathy, etc., are of great importance in the evaluation of patients with chest pain.

Electrocardiogram. The resting electrocardiogram may be completely normal in as many as 25% of patients with angiographically proven coronary heart disease including those with advanced disease and severe symptoms. Of even

Table I

| | Chest pain | | Dizziness vertigo syncope | Response to | | Cardiac auscultation | Abnormal ECG | | Stress ECG | Sx reproduced at bedside |
|--------------------------------------|------------|----------|---------------------------------|-------------|-------------|-------------------------|--------------|--------|---------------|--------------------------------|
| | Typical | Atypical | | Nitrites | Propranolol | | QRS | ST T | | |
| Coronary heart disease | +++ | + | Rare | ++++ | ++++ | - to +++ | common | common | +++ | - |
| Angina with normal coronary arteries | ++ | ++ | Rare | ++ | ++ | - | occasional | common | +++ | - |
| Hypertrophic cardiomyopathy | +++ | + | ++ | + | +++ | - to +++ variable | common | common | +++ | rare |
| Mitral valve prolapse | + | +++ | ++ | + | +++ | - to +++ variable | rare | common | ++ | rare |
| Hyperventilation syndrome | + rare | ++ | ++ | - | + | - | - | rare | + | ++ |
| Esophageal disease | + | +++ | - | + | - | - | - | - | - | - |
| Radiating syn- dromes | + | +++ | + | + | + | - | - | - | - | +++ |
| Chest wall syn- dromes | - | +++ | - | - | - | - | - | - | - | +++ |

In eliciting a history of chest pain five specific characteristics of the discomfort are analyzed: type of pain, location, duration, factors causing pain, and measures which relieve pain.

Type of pain. Angina pectoris is commonly described as a pressure sensation, a tightness, or constricting feeling in the chest. Common similes include like a band being tightened around my chest, or as if someone were standing on my chest. Others will describe it as a burning sensation like indigestion. It is rarely described as sharp or knifelike. Some patients flatly deny that they have any pain whatsoever. Instead, they complain of a suffocating feeling or shortness of breath, which may be misinterpreted as a symptom of pulmonary disease. In the author's experience, these anginal equivalents are more commonly encountered among older people and in diabetic subjects.

It is particularly helpful to observe the patient while the symptom is being described. Frequently, the patient will curl the fingers into a clenched fist over the sternum as he speaks, a sign attributed to the late Dr. Samuel Levine. Others may press the sides of the chest inward with both hands as they search for words to characterize the distress. In each instance, the character of the discomfort varies little with recurrent episodes.

Location of pain. Most commonly, the pain is felt in the center of the chest under the sternum. It may be slightly to the left or less often to the

right of center. Frequently, it will radiate to one or both arms, particularly the left and more often down the inner rather than the outer surface to the elbows, wrists, or occasionally to the fingers. There may be no true arm pain, but instead the arms may be described as feeling heavy or numb. Not uncommonly, the pain will extend into the throat, mandible, or even the maxilla. In other individuals, the pain is in the epigastrium or radiates to the back between the scapulae. In some extra-thoracic pain (i.e., arm or jaw), may exist with no chest discomfort whatsoever.

The location of angina pectoris varies greatly from one person to another, but generally little if at all with recurrent episodes in a given individual. Thus, a person who complains of chest pain in varying locations on different occasions is not likely to have angina pectoris. Another helpful characteristic is that angina pectoris is not well localized. If the painful area can be covered with one finger, it probably does not represent ischemic heart pain.

Duration of pain. Patients with chronic angina pectoris due to coronary artery disease generally obtain relief of their pain within 1 to 5 minutes of rest. Pain which lasts only several seconds or is fleeting is never due to coronary heart disease. Similarly, constant pain lasting days or weeks at a time can safely be assumed to be non-cardiac in origin. It must be emphasized, however, that these limits apply to patients with chronic coro-

suggest mitral valve prolapse as a possible etiology, particularly if the resting electrocardiogram reveals no evidence of a conduction abnormality. Chronic fatigue, anxiety, depression, hyperventilation and a variety of symptoms suggesting a neuropsychiatric origin are common in persons with mitral valve prolapse. On the other hand, aside from appropriate concern for their symptoms, the patient with coronary heart disease and angina pectoris who has good ventricular function generally feels quite well between episodes of ischemic pain.

Physical examination When auscultation reveals a typical mid systolic click late systolic murmur, the diagnosis of mitral valve prolapse is easily established. However, the auscultatory findings in this syndrome may be extremely subtle, evanescent and in some individuals totally unrevealing even on repeated examinations (silent mitral valve prolapse). Not uncommonly careful auscultation in the recumbent and standing position is repeatedly negative while subsequently an unmistakable mid systolic click may appear quite inexplicably. If the clinical syndrome is strongly suggestive of mitral valve prolapse, the diagnosis should never be excluded on the basis of one or two negative auscultatory examinations.

Electrocardiogram Abnormalities of the resting ECG in mitral valve prolapse may be indistinguishable from those observed in either acute or chronic coronary heart disease. When present, the changes most commonly consist of ST segment depression and/or T wave flattening or inversion, particularly in the inferior leads but also in the lateral or right precordial leads.¹² Characteristically, the extent of the repolarization abnormalities may vary considerably, particularly when associated changes in heart rate are observed. The ST-T wave changes of mitral valve prolapse frequently can be differentiated from those of chronic coronary heart disease by their response to a single dose of propranolol.¹³ While repolarization changes due to chronic coronary disease change little 1 to 2 hours following a 40 mg tablet of propranolol, the changes due to mitral valve prolapse often are diminished or may disappear. While this response is not specific for mitral valve prolapse,¹⁴ in the proper clinical setting it may be of great help in distinguishing mitral valve prolapse from coronary heart disease.

Other tests The exercise ECG may reveal a characteristic 'ischemic' response particularly in subjects with some repolarization abnormalities on the resting ECG. While a negative exercise myocardial perfusion scan is helpful in excluding significant underlying coronary heart disease, a positive test has been reported in some patients with mitral valve prolapse and normal coronary arteriograms.¹⁵

Summary Mitral valve prolapse should be suspected in any patient with atypical chest pain, particularly in a female without important risk factors for atherosclerotic disease. Associated symptoms of palpitations, lightheadedness, syncope or conspicuous functional symptoms should immediately alert the physician to this diagnosis, and the presence of repolarization abnormalities on the resting and/or exercise ECG should not be interpreted necessarily as favoring a diagnosis of coronary heart disease. Repeated auscultatory examinations in the supine, standing and squatting positions may be necessary to detect the non-ejection click or when present the dynamic mid late systolic murmur. It should be remembered that there is at present no gold standard for establishing this diagnosis and convincing auscultatory findings should not be overruled by a negative echocardiogram or left ventriculogram.

Hypertrophic cardiomyopathy Hypertrophic cardiomyopathy (HCM) frequently may masquerade as chronic coronary heart disease, particularly when the dominant symptom is angina pectoris. When HCM is associated with left ventricular outflow tract obstruction, a prominent ejection or regurgitant systolic murmur will alert the physician to consider a number of conditions other than uncomplicated coronary heart disease. However, the diagnosis of HCM may be especially difficult when little or no outflow tract obstruction is present and the cardiac examination may reveal few clues to the correct diagnosis. While ischemic heart pain due to inappropriate (or appropriate) hypertrophy of the left ventricle is generally indistinguishable from that due to obstructive coronary disease, often there are useful clues which suggest the former process.¹⁶

Description of pain Although angina pectoris is a common symptom of HCM, it is reported to be the initial symptom in as few as 10% of symptomatic patients.¹⁷ In the obstructive form

greater importance is the observation that *during* chest pain ST segment depression is only found in approximately half of patients suffering angina pectoris at rest.⁴ Thus a normal resting electrocardiogram (random or during pain) is not particularly helpful in the differential diagnosis of ischemic heart pain.

Stress testing. The exercise electrocardiogram has proved extremely useful in the detection of symptomatic coronary heart disease particularly in males. However the ability of this test to confirm or exclude coronary heart disease is greatly influenced by the prevalence of this disease in the population under study. For example in a recent large multicenter study it was found that a positive stress test increased the likelihood of coronary disease by only 6 to 20% and a negative test decreased the likelihood by only 2 to 28% if the pre test prevalence was estimated on the basis of sex and a description of the chest pain syndrome. Expressed differently, when the prevalence of coronary disease is high—i.e. among males with classic angina pectoris—a positive test is highly predictive of coronary heart disease whereas in a group of females with atypical symptoms a negative test is highly predictive of no coronary disease and a positive test would correlate poorly with the presence of coronary disease. When exercise electrocardiography is coupled with either myocardial perfusion scanning or radionuclide cineangiography the sensitivity and specificity of stress testing are greatly enhanced.

Mimics of coronary heart pain

Chest pain syndromes that masquerade as coronary heart disease generally present one or more characteristics which distinguish them from typical angina pectoris. The atypical feature may be a subtle but unmistakable violation in the classic description of Heberden's angina. A convincing pain syndrome may come under suspicion because of its rare association with syncope or paroxysmal rapid heart action. The electrocardiogram may be inappropriate or the patient's posture may suggest a spinal origin of the symptoms. In any case the physician should be particularly alert to unusual aspects of the history or any unexpected findings. Among the many conditions that mimic coronary heart pain a number are particularly common offenders.

Mitral valve prolapse. In some instances the

chest pain syndrome associated with mitral valve prolapse may be indistinguishable from that observed in subjects with coronary artery disease that is a typical effort syndrome with all or most of the features of classical angina pectoris. More often however there are atypical features which alert the physician to a diagnosis other than coronary heart disease.

Description of pain. Rest pain is not uncommon. The duration of pain frequently is variable—at times consistent with classical angina pectoris while at other times lasting for hours at a time. Unlike the situation in the patient with chronic coronary heart disease the location and radiation of the pain may vary in some patients with mitral valve prolapse during recurrent episodes of pain. The response to nitrates often is unpredictable—even in the same individual generally prompt relief of pain is not observed following sublingual nitroglycerin. In the author's experience subjects with mitral valve prolapse often feel better in the recumbent position when they are having chest pain—a characteristic rarely observed in patients with coronary heart disease. This observation is not unexpected when one considers that the relative cardiac dilatation which accompanies recumbency increases wall tension and thus myocardial oxygen requirements aggravating regional ischemia due to coronary disease. Mitral valve prolapse on the other hand is reduced as ventricular dimensions are increased and thus recumbency predictably would lessen the mechanical abnormality of prolapse. Subjects with mitral valve prolapse who have an effort syndrome suggestive of angina pectoris frequently describe spontaneous variations in the severity of the symptoms that are unrelated to the level of activity. They may be relatively free from pain for weeks or months only to experience recurrent bouts of chest pain with relatively little provocation.

Associated symptoms. While patients with chronic coronary disease and angina pectoris may be subject to ventricular ectopy or paroxysmal rapid heart action palpitations are not generally associated with classic angina pectoris. In contrast palpitations are a prominent feature of mitral valve prolapse and commonly coexist with periods of chest pain. Certainly recurrent light headedness or particularly syncope in a person with a chest pain syndrome argues against coronary disease as the cause and should immediately

HCM than to any other condition Q waves in the ECG simulating myocardial infarction may be present in the anteroseptal or inferior leads and have been reported in up to half of patients with HCM¹⁴

Summary In advanced, but as yet unsuspected cases of obstructive HCM the ejection or regurgitant systolic murmur generally leads the physician to consider a valvular lesion which when subsequently evaluated by echocardiography is correctly identified as being due to HCM. However in symptomatic individuals with no murmurs or an innocent systolic murmur careful attention to inappropriate findings in the history, physical examination and ECG is necessary to distinguish the patient with HCM from one with coronary heart disease. Conspicuous dyspnea, symptoms of cerebral ischemia, evidence of left ventricular hypertrophy on the ECG and physical examination (particularly in the absence of radiographic evidence of cardiomegaly) an 'inappropriate' ECG, the absence of risk factors for atherosclerosis—all should suggest the possibility of early HCM in the patient complaining of ischemic heart pain.

Esophageal syndromes Esophageal pain is frequently misdiagnosed as ischemic heart disease although the description of pain is rarely that of typical angina pectoris. However, there are clinical features shared by both diseases which may seriously confound the diagnosis.

Description of pain The common terms used to describe the pain of esophagitis are heartburn, warmth, fullness, pressure, distress, gnawing, a lump—terms quite indistinguishable from those used to describe angina pectoris. Among these perhaps the most common is *heartburn* or its equivalent. When this term is used it is helpful to ask whether the burning sensation more closely resembles *heat* or *acid*. The latter response is quite characteristic of esophagitis but is almost never used to describe ischemic heart pain. Symptoms of esophagitis generally occur after eating and are often initiated or aggravated by recumbency. While this sequence is not particularly common in patients with angina pectoris it is important to remember that with rare exceptions patients with ischemic heart pain too avoid lying flat when they have pain.

The distribution of esophageal pain is quite similar to that of angina pectoris. Most often it is

midline thoracic or abdominal (from the suprasternal notch to the epigastrium) but may extend to the left or right chest, the shoulders, arms and hands, the back or throat. In one series of ninety six patients discomfort was substernal in 70 per cent, abdominal in 67 per cent and radiated to the neck, arms or back in 19 per cent of patients.¹⁵ Although exertional pain has been reported in some patients with esophagitis¹⁶ the possibility of coexisting coronary heart disease in these patients has not been completely excluded.

Esophageal pain simulating ischemic heart pain may also be the consequence of diffuse esophageal spasm or less often achalasia. In a group of 43 patients with chest pain and either normal coronary angiograms or negative exercise tolerance tests, esophageal manometrics revealed high amplitude non peristaltic contractions in one third of the patients.¹⁷ Diffuse esophageal spasm is generally initiated by swallowing particularly of cold liquids, and increased sensitivity to cholinergic drugs and endogenous gastrin may play a role in precipitating symptoms.¹⁸ A favorable response to nitrates in subjects with diffuse esophageal spasm further confounds the problem of distinguishing this condition from angina pectoris.¹⁹

Summary Since both esophagitis and coronary heart disease are common conditions, it is expected that the two diseases will frequently coexist. Indeed the demonstration that one or both conditions are present does not establish with certainty the cause of a given pain syndrome. While endoscopy may indicate that esophagitis is present, a positive esophageal acid perfusion test provides further evidence that esophageal erosion is the source of pain.²⁰ Similarly chest pain and dysphagia precipitated by swallowing cold liquids and associated with high amplitude non peristaltic esophageal contractions strongly suggest that diffuse esophageal spasm is responsible for the symptoms.²¹ In the presence of both coronary and esophageal disease provocative tests may be necessary to ascertain the origin of an atypical chest pain syndrome.

Radicular syndromes The pain of spinal particularly cervical root compression does not frequently mimic ischemic heart pain. Nonetheless, in some instances an effort syndrome virtually indistinguishable from angina pectoris may be

of the disease the most common symptom is dyspnea and in one report this proved to be in the initial symptom in 60% of patients¹⁷ Certainly patients with chronic coronary heart disease and angina pectoris may also complain of dyspnea but it is unusual for this symptom to precede the onset of ischemic pain unless it were misinterpreted as an anginal equivalent. Thus a careful search for HCM should be made in any individual with angina pectoris who has coexisting or antecedent dyspnea which is not easily explained by transmural infarction, cardiomegaly or either regional or diffuse hypokinesis of the ventricle.

While the character, duration and radiation of ischemic heart pain in HCM and chronic coronary heart disease are quite the same, the factors associated with the inception and termination of pain in some instances may be different. For example, it has been reported that the Valsalva maneuver may effect prompt relief of angina pectoris in subjects with coronary heart disease.⁴ Since relief of pain occurs during the strain phase of the maneuver, it was presumed that a decrease in wall force (decreased ventricular pressure and dimensions) and thus myocardial oxygen requirements was responsible for this phenomenon. However, in a subject with obstructive HCM, outflow tract obstruction is provoked by the Valsalva maneuver and thus the procedure may have quite the opposite effect. Occasionally patients with obstructive HCM find that they can obtain relief of their ischemic pain by squatting—a maneuver which increases ventricular dimensions and hence lessens outflow tract obstruction. While subjects with HCM often find nitroglycerin useful in terminating episodes of angina, an adverse response to nitrates may be observed in those with dynamic outflow obstruction. In this circumstance, the reduction in ventricular preload brought about by nitrates may precipitate ischemic pain or may evoke symptoms of cardiogenic cerebral ischemia.

Associated symptoms. As in the case of mitral valve prolapse, the association of chest pain with lightheadedness, dizziness or syncope should always arouse one's suspicion of HCM. Unlike mitral valve prolapse, however, the chest pain is generally ischemic in character and the symptoms of cerebral ischemia are more apt to be effort related. Both atrial and ventricular arrhythmias are common in HCM; the latter not

infrequently present early in the disease and occasionally the first manifestation of HCM may be a fatal ventricular tachyarrhythmia during strenuous physical exertion. Atrial fibrillation tends to be a late complication of HCM and is generally poorly tolerated by the non-compliant hypertrophied ventricle.

Physical examination. The patient with typical ischemic heart pain and a dynamic systolic murmur which is increased in the upright position or during the Valsalva maneuver and which softens during squatting is generally easily identified as having obstructive HCM. The real diagnostic challenge is to identify the patient with HCM who has little or no outflow tract obstruction. In some such patients no murmur is heard in the supine position but a systolic murmur can be elicited by the appropriate provocative maneuvers. In others the only suspicious finding may be a brisk arterial pulse, an abnormal left ventricular impulse or an unusually prominent fourth heart sound which frequently may be felt as well as heard.

Electrocardiogram. Although the ECG was found to be abnormal in all 64 patients with obstructive HCM reported by Braunwald and colleagues¹¹ in 1964, a normal ECG is not uncommon in patients with mild HCM, particularly those with no outflow tract obstruction or those examined early in the course of their disease. Generally, however, the tracing is abnormal, most commonly revealing varying degrees of left ventricular hypertrophy, intraventricular conduction abnormalities or non-specific repolarization changes. However, much more useful in the evaluation of patients with angina pectoris are those abnormalities which don't quite fit the diagnosis of coronary heart disease. For example, broad and/or tall P waves suggestive of atrial enlargement are common in HCM and unusual in patients with coronary heart disease. A slurred inscription of the R wave (delta wave) with or without a short P-R or prolonged QRS interval favors a diagnosis of HCM and this finding too is relatively less common in patients with coronary disease. Indeed, the ECG in HCM often is best described merely as bizarre.

Although electrocardiographic evidence of old transmural myocardial infarction is a hallmark of coronary heart disease, this finding in an asymptomatic young individual is more apt to be due to

HCM than to any other condition Q waves in the ECG simulating myocardial infarction may be present in the anteroseptal or inferior leads and have been reported in up to half of patients with HCM.¹⁸

Summary In advanced, but as yet unsuspected cases of obstructive HCM the ejection or regurgitant systolic murmur generally leads the physician to consider a valvular lesion which when subsequently evaluated by echocardiography is correctly identified as being due to HCM. However in symptomatic individuals with no murmurs or an innocent systolic murmur careful attention to inappropriate findings in the history, physical examination and ECG is necessary to distinguish the patient with HCM from one with coronary heart disease. Conspicuous dyspnea, symptoms of cerebral ischemia, evidence of left ventricular hypertrophy on the ECG and physical examination (particularly in the absence of radiographic evidence of cardiomegaly) are appropriate ECG, the absence of risk factors for atherosclerosis—all should suggest the possibility of early HCM in the patient complaining of ischemic heart pain.

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Summary Since both esophagitis and coronary heart disease are common conditions it is expected that the two diseases will frequently coexist. Indeed the demonstration that one or both conditions are present does not establish with certainty the cause of a given pain syndrome. While endoscopy may indicate that esophagitis is present, a positive esophageal acid perfusion test provides further evidence that esophageal erosion is the source of pain.¹⁹ Similarly chest pain and dysphagia precipitated by swallowing cold liquids and associated with high amplitude non-peristaltic esophageal contractions strongly suggest that diffuse esophageal spasm is responsible for the symptoms.²¹ In the presence of both coronary and esophageal disease, provocative tests may be necessary to ascertain the origin of an atypical chest pain syndrome.

Radiculor syndromes The pain of spinal particularly cervical root compression does not frequently mimic ischemic heart pain. Nonetheless in some instances an effort syndrome virtually indistinguishable from angina pectoris may be

due to thoracic or lower cervical nerve root compression. Generally, however, historical features or provocative maneuvers on physical examination will lead to a correct diagnosis.

Description of pain. Dorsal root pain is generally sharp and piercing, often of lightning character and may be associated with superficial paresthesias. On the other hand, ventral root pain may be a deep, boring, dull discomfort simulating ischemic heart pain. Spinal pain may occur over any part of the chest, the paraspinal area, the axilla, or shoulder girdle and may radiate down the inner or outer aspect of the arm to the fingers. Generally, it is bilateral, but the symptoms from one side of the body most often dominate.

The three major characteristics of root pain are: (1) pain with movement of the body; (2) pain on coughing, sneezing, etc. (Dérjéni's sign); and (3) pain after prolonged recumbency.¹⁸ Shoulder or arm pain may be brought on by rotation of the head to the involved side or flexion of the head to the uninvolved side. Chest pain is often precipitated by bending, hyperextension of the upper spine, or by throwing back the shoulders. Dérjéni's sign is most apt to be observed when the condition is acute. Indeed, the onset of symptoms may be traced, for example, to a particularly vigorous sneeze. The development of root pain after several hours in bed is a common feature of this syndrome and thus may be misinterpreted as nocturnal angina, particularly when associated with other constitutional symptoms (vide infra).

Repeated jarring, such as occurs with running, jogging, driving on a bumpy road, jumping rope, etc., will often provoke root pain and thus exhibit characteristics which may closely resemble angina pectoris. Recently, a syndrome designated cervicoprecordial angina has been described which consists of substernal chest pain simulating angina pectoris but due to cervical root compression.²¹ Exercise-induced pain was present in 14 of 17 patients and 12 obtained prompt relief of symptoms with nitroglycerin. Chest pain was reproduced by a number of provocative maneuvers (vide infra) and all patients had normal coronary arteriograms. The pain was substernal, radiating to the arms and fingers in most patients and usually lasted less than 15 minutes. Relief of symptoms was obtained in the majority of patients by using cervical traction and a six week course of phenylbutazone, although in some

patients laminectomy and foraminotomy were necessary for successful treatment.

Associated symptoms. Paresthesias are common and occasionally precede the onset of root pain. Tingling numbness and stiffness, particularly of the fingers, are generally aggravated by the same maneuvers which provoke pain. Vertigo is not infrequently associated with upper cervical root compression and may be accompanied by nausea. Difficulty in breathing without hyperpnea has been reported in one third of patients with chest pain due to cervical root compression,²² further suggesting a cardiac origin of these symptoms. In rare instances, this peculiar respiratory distress may be the only manifestation of the disease.

Physical examination. The diagnosis of spinal root compression is established by a series of provocative maneuvers. Stretching the arm across the chest while pulling the head toward the flexed shoulder and inhaling deeply is one such maneuver. Pressure applied to the top of the head with the head tilted slightly to one side or the other (Spurling's compression maneuver) is another. Tenderness to deep palpation is an extremely valuable sign. In Davis' series⁴ of 100 patients with chest pain of root origin, moderate or marked spinal tenderness was present in 94% and parasternal or axillary tenderness was present in 98% of those with thoracic root compression.² In one third of patients, firm pressure over the spinous processes evoked referred pain over the anterior or lateral chest wall. Hyperesthesia or hypesthesia to pin prick or light touch may be present. Maneuvers used to identify the thoracic outlet syndromes are also important: the Adson maneuver for the scalenus anticus syndrome (obliteration of the arterial pulse during inspiration while the chin is elevated and rotated to the affected side), the chicken ready to fly sign (abduction and rotation of the upper arms) for the costoclavicular syndrome, and the hyperabduction maneuver for the pectoralis minor and humeral head syndromes.

Summary. Chest pain produced by spinal root compression may on occasion be deep, boring, constricting, short-lived, evoked by physical exercise and relieved by rest and even nitroglycerin. Since symptoms of vertigo, nausea, and respiratory distress may accompany radicular pain, distinction between spinal root pain and angina

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tension are not infrequent during episodes of variant angina. The underlying mechanism responsible for this clinical syndrome is coronary artery spasm. Nonetheless, the majority of patients with variant angina also have fixed coronary arterial lesions with a high incidence of single vessel disease. Despite generally good exercise tolerance, an abnormal exercise ECG is not unusual in patients with variant angina³⁷ and thus it is of limited value in distinguishing typical and variant angina. Nitrates are extremely effective in relieving ischemic pain due to coronary spasm. On the other hand, beta adrenergic blocking agents may aggravate symptoms. Hence, a paradoxical response to propranolol therapy should alert the physician to consider the diagnosis of variant angina.

Chest wall syndromes. Chest pain of musculoskeletal origin is often dull and aching but at times may be sharp or stabbing, particularly when the involved portion of the thorax is moved. Regardless of the character of the pain, it may be embellished by fear of a cardiac origin, giving rise to hyperventilation, palpitations, or a visceral discomfort superimposed upon the primary musculoskeletal pain. With rare exceptions, the diagnosis is easily established by a careful physical examination. Tietze's syndrome, for example, is an uncommon condition consisting of painful, tender and swollen costochondral or sternocostal junctions, sometimes initiated by excessive strain on the rib cage.³ The upper ribs are most commonly affected and pain is frequently aggravated by respiratory straining, weather changes, and perhaps by anxiety. Since physical activity may trigger chest wall pain, the symptoms may be misinterpreted as angina pectoris. Although the course may be prolonged, symptoms are generally easily controlled by reassurance, heat, salicylates, or if necessary, by local injections of xylocaine or steroids. Costochondrodynia is far more common than Tietze's syndrome and differs in that there is no swelling of the involved tender costochondral junction. In these and most other painful chest wall syndromes, the key to the diagnosis is localized tenderness in the painful area or referred chest pain with localized pressure to a portion of the chest wall.³

Pericarditis. Ordinarily, there is little difficulty distinguishing the pain of pericarditis from that of myocardial ischemia. The pleuritic component is

identified by deep breathing, snuffing, or by any abrupt motion of the diaphragm or pleural surface. Rarely, however, acute pericarditis will present with an oppressive, steady chest pain and constitutional symptoms identical to that of patients with myocardial ischemia or infarction. Serum elevations of creatine kinase MB isoenzyme and acute repolarization changes on the electrocardiogram may mislead the physician to favor a diagnosis of infarction. Careful attention to antecedent symptoms of a viral infection, inappropriate fever, failure of the elevated ST segments to evolve a pattern of transmural or nontransmural infarction, a negative hot spot scan, etc., may be necessary to establish that the process is one of epicardial injury rather than coronary vascular disease. Repeated auscultation for a pericardial friction rub and an echocardiographic search for pericardial fluid will help to resolve the issue.

There are many other medical emergencies which may simulate acute coronary heart disease: Pulmonary embolism, aortic dissection, acute pancreatitis, spontaneous mediastinal emphysema, pneumonia—all may be confused with acute myocardial infarction. In these circumstances, however, the presentation is generally a sudden, single event. The response of the physician to these acute situations must be immediate, with a priority of diagnostic procedures based upon those treatable diseases which represent a threat of life. On the other hand, the approach to recurrent chest pain syndromes should be more contemplative, with a special effort made to detect less serious alternatives to chronic coronary heart disease.

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I Electrophysiology of atropine

a Sinus node and the atrial muscle

1 Sinus node automaticity The administration of atropine is a dose of 0.5 mg or more usually accelerates the sinus rate by direct parasympathetic blockade. In addition to this positive chronotropic action atropine given in small doses intravenously can slow the sinus rate or less frequently, may produce a biphasic effect.^{2, 3, 4, 5} The biphasic effect of atropine can also be seen immediately after a higher dose or even following intramuscular administration.⁶ A biphasic response is characterized by initial slowing of the heart rate which is usually followed within 2 to 3 minutes by a positive chronotropic effect. The mechanism underlying the slowing effect of atropine is unclear. Das and colleagues⁷ believe that in addition to producing sinus bradycardia by a central action, low doses of atropine inhibit cholinesterase or may influence the activity of the peripheral sympathetic nervous system.

The effects of atropine on sinus bradycardia and other manifestations of sinus node dysfunction have also attracted attention recently.^{8, 9} The response to atropine is variable. In some patients atropine adequately increases the heart rate whereas in others the response to this drug is barely measurable. This effect of atropine most likely depends on the cause of sinus bradycardia itself. In other words, a minimal response to atropine may be related to intrinsic disease of the SA node while a more satisfactory response suggests an extracardiac origin or so called physiologic bradycardia.¹⁰ The usefulness of atropine in the evaluation of sinus node dysfunction will be discussed in more detail below.

Automaticity of the SA node can also be evaluated by measuring the sinus node recovery time (SNRT) which is the duration of atrial asystole after rapid atrial pacing is discontinued. It is believed that this method is more sensitive than pharmacologic tests in the differentiation of intrinsic sinus node dysfunction from physiological bradycardia. The pause in atrial activity after discontinuation of rapid atrial pacing is mainly a measure of the functional status of the SA node and is longer in patients with decreased SA node automaticity than in those with normally functioning sinus node. According to some authorities, however, the effect of rapid atrial pacing is more complex than simple inhibition of the automaticity of the SA node and the sensitiv-

ity of this test for sinus node dysfunction is low.^{11, 12, 13}

In general, atropine shortens the SNRT in normal individuals and in most patients with sinus node dysfunction.^{2, 10, 13, 14} Atropine paradoxically prolongs the SNRT or produces a transient AV junctional rhythm when given to some patients with sinus node dysfunction.¹⁵ This paradoxical effect on SNRT may be mediated through the effect of atropine in improving sinoatrial conduction. Because the number of impulses entering the SA node after atropine is greater the SA node itself will be suppressed. Reiffel et al.¹⁶ suggested that this paradoxical effect of atropine on the SA node could also result from concealed conduction or from altered conduction within the SA node.

2 Sinoatrial conduction Impaired automaticity of the SA node is only one function which can underlie sinus node disease. Strauss and co-workers¹⁷ have suggested that another abnormality, impaired sinoatrial conduction (SAC) may be involved. This assumption has not been accepted by all. For instance, Scherf¹⁸ and Dighton¹⁹ believe that SA block is a manifestation of a nodal disease rather than of true conduction defect. On the other hand, electrophysiologic observations and experimental studies by Strauss and Bigger²⁰ point to the existence of true sinoatrial block.

Sinoatrial conduction time can now be measured only indirectly using artificial atrial premature stimulation²¹ or in patients with atrial parasystole as described by Langendorf and colleagues.²² By this method²³ the sinoatrial conduction time is calculated to be the difference between the basic cycle and the return cycle following introduction of an artificial atrial premature beat. According to this concept, antegrade and retrograde conduction between the SA node and the atria are the same and the artificial impulse only resets the SA node and has no influence on its automaticity.

The effect of atropine on sinoatrial conduction time has also been studied by several groups of workers. Among them, Bissett and co-workers²⁴ and others^{25, 26} demonstrated a shortening of the sinoatrial conduction time after the administration of atropine to subjects with normal SA node function while Reiffel and Bigger²⁷ also showed improved sinoatrial conduction time in patients with sinus bradycardia. On the other

Appraisal and reappraisal of cardiac therapy

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The effect of atropine on cardiac arrhythmias and conduction Part 1

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The effects of atropine on cardiac rhythm have been known since 1912 when Robinson and Draper¹ abolished atrial premature beats with the drug and 1915 when Wilson induced atrioventricular (A-V) dissociation. The latter results established a pattern of investigation for early workers who then concerned themselves with the effects of atropine on A-V conduction.² More recently since the report of Agress and Binder,³ the effectiveness of atropine in acute myocardial infarction complicated by bradycardia was investigated intensively. In subsequent studies with atropine Thomas and Woodgate⁴ and Harris and Bluestone⁵ using atropine corrected both bradycardia and hypotension occurring in patients with myocardial infarction and in a more extensive series of patients Adgey and colleagues⁶ found that atropine corrected bradycardia and hemodynamic abnormalities and also suppressed ventricular premature beats. As a result this clinical setting became the prime indication for atropine.

Following introduction of intracavitary electrocardiography and pacing techniques the usefulness of atropine in the management of patients with sinus node dysfunction was assessed and its effect on the electrophysiological functions of the sinoatrial (SA) and atrioventricular (AV) nodes was analyzed.

The number of studies reported increased and inevitably some confusion about the usefulness

of atropine also arose as some studies led to apparently conflicting data and note was made of hazards arising from atropine's use.

Accordingly in this review we will summarize the electrophysiological effect of atropine on the cardiac conduction system and myocardium and attempt to establish criteria and guidelines for its use and explain some of its seemingly conflicting and paradoxical effects.

Best known of the cardiac effects of atropine is its ability to increase heart rate and facilitate A-V conduction by its vagolytic action on the sinus node.⁷⁻⁹ However atropine also exerts a direct influence on the function of the AV junctional tissue¹⁰ and the subjunctional components of the specialized conducting system.¹¹ Some of the other effects of atropine are indirect and are probably related to unopposed action of the sympathetic nervous system or simply to an increased heart rate. The response to atropine also depends on the varying sensitivity of different levels of the specialized conducting system to autonomic stimuli. In fact under circumstances to be described not all components of the specialized conducting system will respond to vagal stimulation or blockade. Furthermore the differing sensitivity to atropine of the various structures of the specialized conducting system may lead to unpredictable and apparently paradoxical effects.

The amount of atropine necessary to produce complete blockade of the parasympathetic nervous system is uncertain. According to some workers 20 mg of atropine should inhibit the vagus nerve while Jose¹² and Chamberlain and co-workers¹³ believe that as much as 3 to 6 mg of atropine is needed to block the vagus completely.

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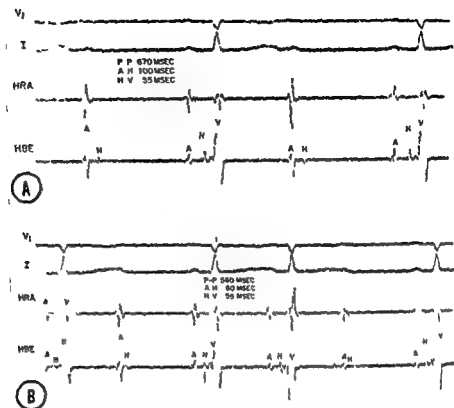


Fig 2 (Patient 2) The effect of atropine on second degree AV block. From the top to bottom Lead V_1 , I high right atrial electrogram (HRA) and His bundle electrogram (HBE). A there is a 2:1 AV block. Each atrial deflection is followed by an H spike confirming the presence of a block below the AV node. B five minutes after the administration of 10 mg of atropine the 2:1 AV block changed to 3:2 AV block.

the pacemaker localized in the distal part of the His bundle can also respond to autonomic stimuli.^{47, 48}

2 Atrioventricular conduction. Facilitation of AV nodal conduction by atropine in patients with normal AV nodal conduction is a well known effect. Akhtar and colleagues³⁷ and others³⁸ demonstrated that atropine improves AV nodal conduction and decreases both the effective and functional refractory period of the AV node. Further, second degree AV block is achieved at higher pacing rates after the administration of atropine. Shortening of AV nodal conduction time is manifested regardless of the dose of the drug administered.⁴

The effects of atropine on first degree AV block from different causes are variable and unpredictable.⁴⁹ In second degree AV block, the response to atropine is more consistent. In general, type one second degree AV block will disappear after the administration of atropine, while the drug tends to be ineffective in type two second degree AV block.^{49, 50}

Dual AV nodal pathway (DAVNP) is a not uncommon condition characterized by the pres-

ence of two intranodal pathways with different refractoriness and conductivity. One pathway which conducts the atrial impulse faster usually has a longer effective refractory period, whereas the second pathway through which the impulse travels more slowly tends to have a shorter effective refractory period. Neuss and co-workers⁴⁹ studying the effect of atropine in eight patients with DAVNP abolished the DAVNP in four, while in three patients the drug was ineffective and in one case DAVNP was unmasked by atropine. Recently, Akhtar and co-workers⁵⁰ reported five patients in whom neither atrial pacing nor atrial extrastimulation induced a paroxysm of supraventricular tachycardia at rest, while following administration of atropine, premature beats initiated a supraventricular tachycardia. It is likely that in this study atropine unmasked a DAVNP which is now assumed to be a necessary electrophysiological abnormality for initiation of a reentrant tachycardia.⁵¹

c His Purkinje system and ventricular muscle.
1 Automaticity of the His Purkinje system. The influence of the parasympathetic nervous system

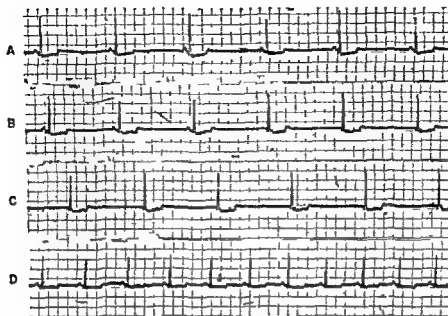


Fig 1 (Patient 1) Atropine-induced AV junctional rhythm A sinus bradycardia with a rate of 37/minute B and C two minutes after the administration of 10 mg of atropine there is an AV junctional rhythm and AV dissociation D sinus rhythm at a rate of 74/minute resumes five minutes after the administration of atropine

hand Dhingra and associates²⁷ found that while atropine shortens sinoatrial conduction time in normal patients it does not have this effect in the presence of sinus node dysfunction.

3 Atrial muscle Reports of the effect of atropine on the refractoriness of atrial muscle in man are few and also conflicting. Some authors²⁸ found shortening of the effective refractory period of the atrial muscle in normal individuals after atropine but others have not been able to confirm these findings²⁷ nor does atropine significantly influence the effective refractory period of the atrial muscle in patients with sinus node dysfunction according to Dhingra and co workers.³

b Atrioventricular junction

1 Atrioventricular junctional pacemaker Atropine stimulates the atrioventricular junction pacemaker in normal patients and in those with sinus nodal disease. In normal subjects the increased activity of the AV junctional pacemaker becomes evident immediately after the administration of atropine when the drug temporarily suppresses the SA node and stimulates the subsidiary pacemaker.

This effect is demonstrated by the following patient. A 72 year old man was admitted because of syncope. The ECG on admission showed sinus bradycardia with a rate of 37/minute (Fig 1A).

Two minutes after the administration of 10 mg of atropine there was a slight decrease of sinus rate after which AV dissociation appeared (Fig 1B and C). Five minutes following the administration of atropine the sinus rhythm increased to 74/minute (Fig 1D) and the AV dissociation was abolished.

In some patients with sinus node dysfunction the resulting AV junctional rhythm can last for as long as 3 hours. The mechanism for this sustained AV junctional rhythm is not well understood. We suggest that in these patients the SA node becomes unresponsive to automatic stimuli, permitting the effect of atropine on the AV junctional pacemaker to become dominant.

Atropine may also be useful in helping to localize the level of the block in patients with complete AV block and narrow QRS complexes. Narula and associates²⁹ studying the effect of atropine in 11 patients with these electrocardiographic features noted that atropine increased the rate of the escape pacemaker in five patients and had no effect on the subsidiary pacemaker in the remaining six. They postulated that in patients who responded to atropine the subsidiary pacemaker was in the AV junction while the nonresponder had the escape pacemaker within the His bundle. These results have been confirmed^{6, 30} but recent case reports suggest that

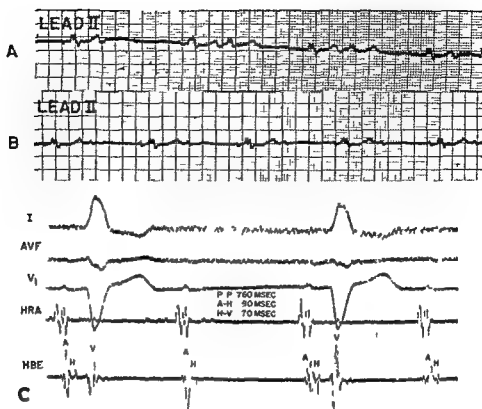


Fig 4 (Patient 3) The effect of atropine on second degree AV block A atrial bigeminy the atrial beat after the first and fourth beat is blocked B administration of 10 mg of atropine suppresses the atrial premature beats and produces a 2:1 AV block C from top to bottom Lead I aV_r V₁ high right atrial electrogram (HRA) and His bundle electrogram (HBE) 2:1 AV block localized below the AV node is demonstrated

with shortening of the A-H interval (Fig 2B). After an acute inflammatory or ischemic disease had been ruled out by appropriate study the patient underwent exercise testing. The resting ECG showed 3:2 AV block (Fig 3A). During exercise there were short episodes of 1:1 conduction despite a rapid sinus rate (Fig 3B, C and D).

Finally, atropine also has a paradoxical effect on AV conduction by causing AV block or increasing a pre-existing conduction abnormality. Most patients responding in this manner had conduction defects below the AV node⁷ or acute myocardial infarction. The apparent paradoxical effect of atropine in patients with subnodal conduction defect probably results from an increased sinus rate which unmasks the conduction abnormality below the AV node.

Our third case illustrates this effect of atropine. The patient is an 82-year-old man seen in the emergency room because of dizziness. The ECG showed sinus rhythm with the rate of 140/minute and frequent atrial premature beats. One of

them blocked. A rhythm strip (Fig 4A) shows atrial bigeminy. Administration of 10 mg of atropine increased the sinus rate to 83/minute, suppressed the atrial irritability and initiated a 2:1 AV block (Fig 4B). Thirty minutes after the development of the AV block, a His bundle electrogram was recorded (Fig 4C). The intracavitary recording demonstrated the conduction defect below the AV node. Atropine not only suppressed the APC⁸ but also uncovered an AV conduction disturbance.

Worsening of AV conduction or development of paroxysmal AV block in patients with acute myocardial infarction after the administration of atropine has been reported.^{11,12} The localization of AV block caused by atropine in these patients was not confirmed by His bundle recording and therefore we do not know at what level the AV conduction was impaired. Because some of these reported patients had inferior myocardial infarction in which the block is usually localized in the AV node, it is assumed that atropine caused a conduction disturbance within the AV node.

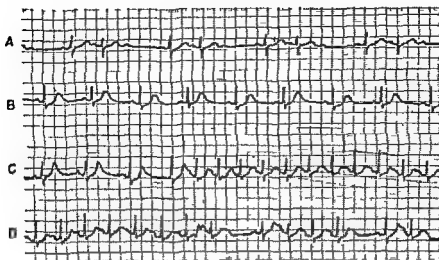


Fig 3 (Patient 2) The effect of exercise on second-degree AV block Lead V A resting ECG shows 3:2 AV block with an atrial rate of 93/minute B during exercise the atrial rate increases to 135/minute and the AV block changes from 3:2 to 2:1 C and D transient 1:1 conduction is noted at the same atrial rate as in B

on the automaticity of the His Purkinje system was postulated in patients with advanced AV block and idioventricular rhythm by Schwartz and de Sola Pool⁸ who demonstrated that atropine increases the idioventricular rate and also suppresses ventricular irritability in patients with third degree AV block. Following a renewal of interest in this problem recent studies suggested that the subnodal portion of the His Purkinje conducting system is indeed under parasympathetic influence. Bailey and co workers¹² showed that in *in vitro* preparations acetylcholine decreased phase four diastolic depolarization in the proximal part of the intraventricular conducting system. Danilo and associates¹³ demonstrated the same effect on the Purkinje system and also showed that atropine blocks the effect of acetylcholine on the intraventricular conducting system.

Existence of parasympathetic innervation of the subjunctional specialized conducting system was also confirmed by Kent and co workers¹⁴. The response of the intraventricular conducting system to parasympathetic stimulation is further supported by Waxman and Wald¹⁵ who were able to interrupt ventricular tachycardia in humans by vagal stimulation. Finally the previously discussed response of the subjunctional pacemakers to autonomic stimuli is consistent with these experimental findings. "On the other hand Narula and colleagues¹⁶ and others¹⁷ believe that the subjunctional pacemakers are insensitive to vagal stimulation.

2 His Purkinje system conduction The effect

of atropine on subjunctional conduction is also unclear. It is generally believed that a conduction disturbance below the AV node will not improve or may even be aggravated after the administration of atropine.¹⁸

Patients with conduction disturbance within the His bundle are the most suitable group in which to test the effect of atropine on subnodal conduction. According to Gupta and colleagues¹⁹ there are patients with *intra Hisian* block in whom atropine improves conduction but the response to atropine of the subjunctional conducting system is less predictable. The reason for this variable effect of atropine on the conduction through the His bundle is unclear. One can speculate that the response to atropine depends on the site of conduction defect within the His bundle. That is to say atropine is more effective in a proximal than in a distal *intra Hisian* block.²⁰

The effect of atropine on AV conduction in our next patient supports our contention that there are important subjunctional parasympathetic effects. The patient is a 46 year old man with a history of dizziness of one day duration. The electrocardiogram on admission showed 2:1 AV block. Subsequently a His bundle electrogram was recorded before and after 0.1 mg of atropine following which a temporary pacemaker was inserted into the right ventricle. The His bundle recording demonstrated a block below the AV node (Fig 2A). Administration of atropine increased the heart rate from 89/minute to 107/minute and the block changed from 2:1 to 3:2.

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Fig 5 (Patient 4) The effect of atropine on the sinus node and AV conduction in a patient with inferior myocardial infarction. Lead I. A before administration of atropine there is sinus bradycardia at a rate of 36/minute and sinoatrial block. The fourth and seventh beats are AV junctional escape beats. B the sinus bradycardia is replaced by AV junctional rhythm at a rate of 36/minute after the administration of 1.0 mg of atropine. C the AV junctional rhythm lasted for one minute after which sinus rhythm complicated by high grade AV block appeared. Only the fifth sinus impulse is conducted into the ventricle. The ventricles were controlled by an AV junctional pacemaker. D the AV block persisted and the QRS complex became wide measuring 0.11 sec. The rates of the narrow and wide QRS complexes were the same (39/minute). E the first two narrow QRS complexes precede ventricular premature beats. Elsewhere the QRS complexes are wide. From C to E there is a progressive increase of the atrial rate from 60/minute to 100/minute.

However this assumption requires confirmation because the situation is probably more complex and atropine may unmask impairment of conduction at more than one level as is indicated by our fourth patient.

The patient, a 42 year old man, was admitted with an acute inferior myocardial infarction. On the tenth day in the hospital after an uncomplicated initial course the patient developed syncope. An ECG taken at that time showed sinus bradycardia with a ventricular rate of 36/minute, sinoatrial block and AV junctional escape beats (Fig 5A). Atropine in a dose of 0.5 mg was ineffective and therefore a second dose of 0.5 mg of atropine was administered after which the sinus rhythm was transiently replaced by AV junctional rhythm with a similar ventricular rate (Fig 5B). Following resumption of sinus rhythm (60 to 80/minute) an advanced AV block developed together with intermittent widening of the QRS complex and ventricular premature beats (Fig 5C, D and E). The increased duration of the QRS could be due either to an idioventricular rhythm or to aberrant conduction of the AV junctional beats. Because the heart rate did not change significantly, aberrant conduction is a

more likely explanation for the wide QRS complex than is an idioventricular rhythm. A temporary pacemaker was inserted into the right ventricle and the patient made an uneventful recovery. In this case atropine improved sinoatrial conduction and sinus node automaticity and at the same time unmasked latent AV and intraventricular conduction disturbances. This second effect of atropine occurred after the drug increased the sinus rate. The exact localization of the block is uncertain without His bundle recording. The conduction defect was probably localized below the AV node because both AV and intraventricular block were present.

According to Guss and colleagues¹ atropine does not significantly influence the refractoriness of right ventricular muscle. This observation is consistent with the findings of Kent and co-workers² who showed that the parasympathetic innervation of ventricular muscle is sparse in comparison to the rich cholinergic innervation of the intraventricular conducting system.

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Of papillary muscle dysfunction murmurs

It was not made sufficiently clear that the murmur of papillary muscle dysfunction can have almost any imaginable characteristics with regard to both the time course of intensity and/or frequency. The French clinicians were correct when they referred to the heart sounds and murmurs as noises. The only characteristics common to all papillary muscle dysfunction murmurs are that they originate from the mitral valve and are systolic in time. Thus their location and transmission and referral are the same as for any murmur of mitral insufficiency. The time course of the level of the pressure gradient across the mitral valve and the size and shape of the orifice through which the leak occurs and the time course of all three of these factors with respect to each

other will determine as expected the characteristics of the murmur of papillary muscle dysfunction. This is also true of all heart murmurs.

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Pacemaker annihilation: diagnostic and therapeutic implications

Over the years clinical cardiologists have searched for electrocardiographic clues to distinguish between reentrant and pacemaker mechanisms of cardiac arrhythmias. For example, it has been assumed that if a properly timed stimulus applied through external or intracardiac electrodes can terminate an episode of tachycardia, then the mechanism must have been reentrant; a single stimulus would not be expected to suppress the spontaneous firing of an ectopic pacemaker. Unfortunately, recent electrophysiological experiments have demonstrated that the validity of this diagnostic criterion is questionable.

Spontaneous pacemaker activity in cardiac pacemakers is characterized by rhythmic oscillations in their membrane potential. The mechanism of pacemaker depolarization in cardiac Purkinje fibers, sinoatrial nodal cells, and in working myocardial cells undergoing spontaneous activity induced by steady depolarizing current has been studied by voltage clamp experiments. In all cases, pacemaker activity has been attributed to a cyclical voltage-dependent potassium current. This current has nonlinear features, such as anomalous rectification and negative conductance, and it gives the pacemaker feedback characteristics that are common to other biological oscillators. Spontaneous activity in cardiac pacemakers can be modulated by stimuli from their natural surroundings.

In general, if the spontaneous firing of a pacemaker is kicked off its stable cycle by a brief tonic stimulus, or by a transient vagal burst, it eventually resumes its previous rhythmic activity with the same cycle length but generally

with a new phase in relation to the previously unperturbed rhythm. The magnitude and direction of this phase shift depend on the time of stimulus application. This is illustrated in Fig. 1A which shows a phase response curve (PRC) obtained from a spontaneously beating Purkinje fiber mounted in a sucrose gap chamber (for method, see Ref. 9) and firing at an average basic cycle length (BCL) of 1,600 msec (maximum diastolic potential MDP = -87 mV). The curve shows delays and accelerations (positive and negative Δ BCL, respectively) effected by brief depolarizing current pulses (500 msec, 0.8 μ A) as functions of the time of stimulus application expressed as percent of BCL.

In most experiments these effects are transient and the pacemaker rapidly returns to its free-running activity. However, in some preparations pacemaker activity can be terminated with a single stimulus applied at the proper time. Figure 1B shows analog records from the same experiment when the membrane potential of the pacemaker was continuously depolarized with a bias current step of long duration. Under these circumstances MDP decreased to -77 mV and the pacemaker was beating at an average BCL of 1,450 msec in the steady state. As the pacemaker cycle was scanned by a depolarizing current pulse of the same duration and magnitude as in panel A of Fig. 1, a critical phase in the cycle was reached during which current pulse application was sufficient to progressively larger and eventually reached threshold (Fig. 1, panel B2) or they damped and resulted in complete annihilation of pacemaker activity (panel B3). Pacemaker activity

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Common sense and clinical chemistry

The evolution of clinical chemistry over the past 20 years has been a curiously uncontrolled process. Clinical chemistry is an applied science whose primary function is to provide information which is relevant to the diagnosis and management of patients. Decisions about which constituents of body fluids should be measured are based on the ease with which measurements can be made and the clinical relevance of the tests. Unfortunately, the former consideration has always weighed more heavily than the latter. As a result of the spectacular advances in methodology and automation since the 1950s many biochemical substances can now be measured with great speed and precision. The exponential growth in the workload in clinical chemistry departments which shows little sign of abating testifies to the enthusiasm with which these advances have been welcomed by both clinicians and clinical chemists. Unfortunately, both groups appear to have lost sight of the need for at least a modicum of clinical relevance to justify the explosion. Consequently the exponential decay rate of the proportion of tests which serve any real purpose is higher than the workload growth rate.

In my own hospital in the absence of any significant changes in the management of water and electrolyte balance the numbers of plasma sodium measurements have risen by 600% over 13 years. Apart from the steady rise prompted by the assumption by clinicians that they have been negligent if any patient escapes from the hospital without an electrolyte estimation there were sharp increases in 1960 when with the introduction of a new flame photometer it became automatic that the sodium was measured whenever the blood urea nitrogen was requested which doubled the sodium numbers overnight and in 1972 when a Technicon multichannel electrolyte analyzer was purchased.

The workload in almost any general hospital today will be too large and the technical staff too small to make it feasible to be totally selective in biochemical tests but it is important to differentiate groups of investigations which have some functional biochemical relationship from those which are related only because of the organization of analytical machinery. It is justifiable to report plasma sodium potassium chloride bicarbonate and urea nitrogen together when

ever one of these tests is requested because of the way in which deviation from normality of each is often related to deviations in the others. When however liver function tests are provided gratuitously whenever electrolytes are requested or the serum uric acid is automatically added to a bone profile because it is felt that all tests should be part of a profile and joints are anatomically related to bones then the clinical disadvantages rapidly outweigh the initial convenience to the laboratory and subsequently the laboratory is swamped with unnecessary repeat requests.

The whole philosophy of biochemical screening is based on a failure to relate biochemical findings to the management of disease. It is often suggested that one aim of clinical chemistry should be to detect and follow up disease as early as possible. Ischemic heart disease is cited as an example where a dedicated approach would be both individually beneficial and economically sound. This proposal confuses theory and fact and ignores practicality. There is no clearly recognized biochemical predictor of ischemic heart disease, no clear line of prevention and no way of persuading patients to eat less, give up smoking, worry less and exercise more even if one were convinced that these were effective measures and the implementation of such a management program would provide more than full time occupation for all the country's doctors and nurses.

Even in diabetes mellitus which is the disease most likely to be revealed by biochemical screening and where there is at least a clearer although by no means absolute relationship between a single biochemical test, the blood glucose and the incidence of cardiovascular, renal and neurological complications there is still no evidence that the detection of an elevated blood sugar before the onset of clinical signs is of a value either in the short or in the long term.

There have been several reports of the almost total failure of communication elicited by the battery of unspecified abnormal results produced with the profile screening. The volume of work which this approach itself generates is considerable. Of 2000 patients who had an admission profile of 14 biochemical tests 36% had at least one unexplained abnormal result for a test which had not been requested. The immediate

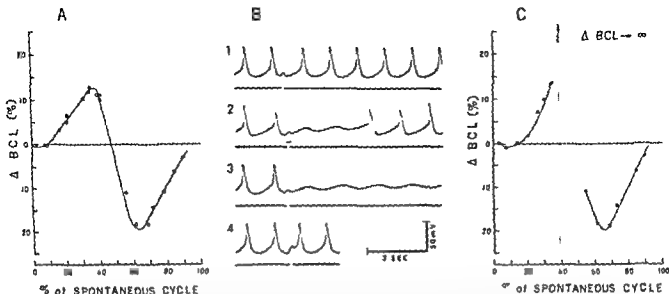


Fig 1 Phase resetting behavior of a Purkinje fiber pacemaker. A Phase response curve (PRC) obtained from a Purkinje fiber sucrose gap preparation by scanning the pacemaker cycle with brief subthreshold depolarizing current pulses. B Microelectrode recordings from the same preparation using current pulses of the same duration and magnitude but following a change of the steady state maximum diastolic potential to -60 mV by the application of bias current. C PRC from a complete scan in the run illustrated in panel B. The vertical arrow indicates the phase of the spontaneous cycle at which annihilation occurred (58°).

could be restored by the application of a second brief pulse of larger intensity. If the same stimulus (200 msec, $0.8 \mu A$) was applied at a different phase in the cycle it merely delayed (Fig. 1, panel B1) or accelerated (panel B4) subsequent discharges. Panel C illustrates the PRC obtained under these conditions and shows that the annihilation phenomenon ($\Delta BCL \rightarrow \infty$) was only observed when the perturbing stimulus was presented between 36 and 52% of the spontaneous cycle. When the duration or the amplitude of the current pulse was changed or when the membrane potential was returned to more negative levels (-84 to -91 mV) by decreasing the strength of the bias current, pacemaker activity could not be terminated with a single stimulus and the PRC returned to its original shape (Fig. 1A).

The phenomena we have just described are not unique to the isolated Purkinje fiber. We have been able to annihilate the spontaneous rhythm of isolated SA nodal cells. G. Ferrer (personal communication) has obtained similar results in working muscle preparations in which repetitive activity was induced by depolarizing bias current. And Wit and Cranefield have reported a similar phenomenon in simian mitral valve fibers undergoing triggered automatic activity. In fact phase resetting behavior and annihilation phenomena have been observed in a variety of self-sustaining oscillatory systems including circadian rhythms, neuronal pacemakers, and biochemical oscillators. Common to all systems is the fact that an exact combination of stimulus timing, duration, and magnitude annihilates the pacemaker rhythm.

Although direct extrapolation is difficult, the experimental and clinical implications of these phenomena are obvious in terms of mechanism, diagnosis, and treatment of cardiac arrhythmias. As we have suggested in previous studies, classical criteria to differentiate between reentrant and pacemaker mechanisms based on the analysis of the electrocardio-

gram will have to be re-examined. The experiments outlined above further strengthen this contention and they demonstrate together with the experiments of Ferrer and co-workers and of Wit and Cranefield that the fact that a single stimulus can terminate a tachycardiac arrhythmia can no longer be taken as an absolute proof of reentry. Furthermore, the existence of these phenomena in cardiac pacemakers should be taken into account when analyzing the success or failure of therapeutic measures such as the drug treatment of ventricular parasystolic and other extrasystolic arrhythmias.

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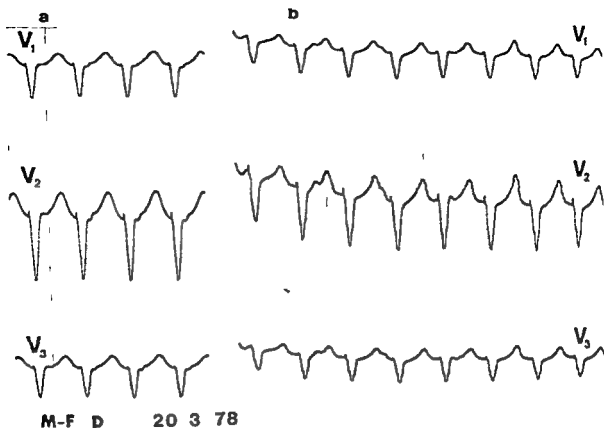


Fig 1 Patient M-F D ECG recordings *a* before and *b* after lignocaine blocking of the left stellate ganglion (intracavitary stimulation at 120 impulses per minute). There is shortening of the QT interval after lignocaine

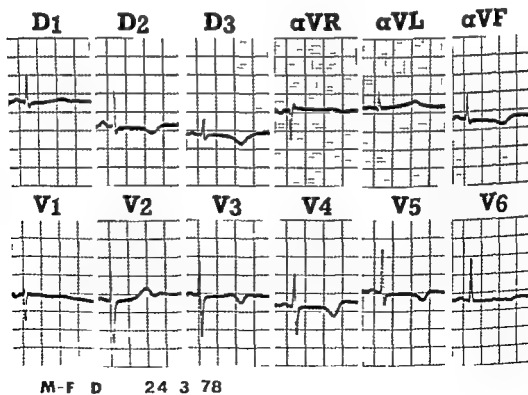


Fig 2 Symptomatic at 44, 1 ECG after left stellectomy (QT interval = 0.37 sec)

implication is that every third profile will if the clinician reads the report generate the fourth. However five years later follow up of 200 of this group of patients revealed that only three had results indicative of presymptomatic disease and the authors voiced doubts about the prognostic significance of early diagnosis even in these. In this situation clinicians confronted with an unexpected laboratory value which deviates from the normal range rapidly learn to consider it clinically insignificant and ignore it. After repeated exposure to such values they become increasingly prone to ignore everything the laboratory reports, and this includes those results which require action.

On the basis that information to be transmitted to clinicians should have direct relevance to the management of their patients its quantity should be as small as possible consistent with this aim. The clinical chemist's ability to generate adequate laboratory information even in relation to discretionary tests is already very considerably greater than the clinician's ability to use it. The charitable urge to produce information which has not been requested because it can easily be made available should be resisted as far as possible. Manufacturers of analytical machinery have stepped in with glee to profit from the loss of control of the medical profession over the investigation of their patients and have increased the momentum with which we are racing in the wrong direction by producing ever larger machines with ever more channels. It is legitimate for the manufacturers to think only in terms of the money they can make. Doctors should be swayed by other considerations of which not the least important is common sense.

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Romano-Ward syndrome treated by left stellatectomy and intracavitary stimulation

In the June 1976 issue of *THIS JOURNAL* we reported the case of a patient with congenital QT segment prolongation (Romano-Ward syndrome).

In view of the small number of reported cases and the uncertainties regarding the accurate treatment of that ominous disease responsible for sudden death by "torsades de pointe" we think it interesting to report briefly the outcome of the original mode of therapy applied in this case.

The case of the patient M F D was satisfactory until January 1978 with occasional palpitations.

In spite of the sustained administration of propranolol 20 mg 4 times daily and digitalin 0.1 mg five times weekly she was seized in February 1978 by short lived convulsions. In March 1978 severe and repeated spells of "torsades de pointe" were discovered which were abolished by a temporary intracavitary stimulation. After lignocaine blocking of the left

stellate ganglion a shortening of the QT interval was observed from 0.48 to 0.47 sec under intracavitary stimulation at 100 impulses per minute (Fig 1). A left stellatectomy involving the inferior two thirds of the ganglion was then performed by the axillary way which resulted in an incomplete Horner's syndrome (pupillary constriction without enophthalmos or ptosis).

Subsequent ECG recordings showing a persistent lengthening of the QT interval between 0.52 and 0.60 sec (Fig 2) the installation of a permanent intracardiac pacemaker was decided upon with a programmable Cordis Omniscancer set at 90 impulses per minute. This procedure was followed by the complete disappearance of syncope and palpitations. Various ECGs and 24 hour ECG recording (Holter monitoring) revealed a good control of the rhythm by the implanted pacemaker with rare conducted atrial beats whose QT inter-

To the Editor:

The ecology of *Mytilus* is related to the width of the stable interval in the genotype. In *Mytilus*, the stable interval has a wide range of values, and this is reflected in the phenotypes of the genotype.

Our patient presented two years ago with a 1
hemiplegia, and following a rather extensive
investigation which ruled all known causes for an
ulnar nerve palsy out, she was diagnosed as
111. At this time her glaucoma was not
763 mg/dl in an all-time high of 170 mg/dl
and its turnover was 111 mg/ml day for an all-
time high of 170 mg/ml day. The patient at this time
was when she was presently 111 mg/dl
decrease in the value of the left eye to 111 mg/dl
even angiography revealed the existence of the
111.

8. Ho? ʔtʔ
 H H ʔtʔ
 9. ʔʔw fʔ ʔtʔ
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Doʔ tʔw nʔ ʔtʔ fʔ
 fʔ l n ʔ ʔtʔ nʔ
 fʔ w h fʔ d f ʔtʔ

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July 21, 1964

[illegible]

1 My name is [redacted] I was born [redacted]
[redacted] I am currently [redacted] years old
and my current address is [redacted]

2 My name is [redacted] I was born [redacted]
I am currently [redacted] years old
and my current address is [redacted]

7499

These papers were not in use at the time of
liberation

[illegible]

T. the first

The Harvard II, in his historical record we begin to find a hint of deeper spiritual truth has reached some of those who have posed the question II suggest that a very real even so there are not in terms of mortal's important. If we are in a survey of the final features of punishment it is in Hell and its legions found that more than a quarter of the subjects with anger graphically proven emboldened

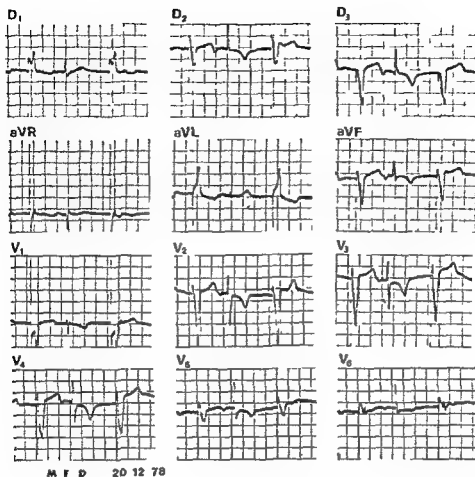


Fig 3 Same patient as in Fig 1. The ECG shows good stimulation by the pacemaker and conducted beats with a normal QT interval.

val was normal (Fig 3). To our knowledge this is the first report of left stellate ganglionectomy associated with the implantation of a pacemaker with a relatively high preset rate of stimulation. This kind of treatment seems to be logical and effective. Left stellatectomy alone, while being the treatment of choice in the Romano Ward syndrome of some authors, resulted for others in inconstant improvement, short lived shortening of the QT interval, or even complete failure.

On the other hand, intracavitary stimulation prevents bradycardia common in the Romano Ward syndrome and increased by the beta blocking agents.

Slow cardiac rates induce asynchronous repolarization and ectopic beats. Finally, this report points to the important part played by sympathetic imbalance in the genesis of the Romano Ward syndrome.

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lower limb symptoms. It appears then that asymptomatic thrombi can commonly give rise to pulmonary emboli. It is not yet possible to predict which emboli are likely to embolize and therefore for the present it is rational to consider prophylactic measures which reduce the incidence of all thrombi symptomatic or not.

Dr Blaisdell points out that the ^{125}I fibrinogen uptake test commonly used in clinical studies of thrombosis is less sensitive in the thigh and pelvic veins than it is in the calf. The test is often criticized on this basis since most pulmonary emboli are said to originate in the larger, more proximal veins. However, in an extensive autopsy series, Havig found that among 120 patients with pulmonary embolism the most proximal thrombi were below the knee in 43 cases. Twenty-five percent of lethal emboli originated in the calf. Furthermore, it appears from venographic and autopsy studies that the majority of thrombi arise in the deep veins of the calf. Most thrombi involving the popliteal, femoral and iliac veins are continuous with, or associated with, calf vein thrombi and would therefore be detected by the ^{125}I fibrinogen test. In view of this, we conclude that for clinical trials of prophylactic regimens the ^{125}I fibrinogen uptake test remains the method of choice for detecting deep vein thrombosis.

A very useful follow up test to the ^{125}I fibrinogen scan is radioisotope venography using radiolabelled macro aggregates of albumin. This is less invasive than conventional x-ray venography and appears to be as accurate in the thigh and pelvic veins. The radiolabelled particles cleared from the leg will also provide a perfusion lung scan. It is thus a particularly valuable follow up to a positive ^{125}I fibrinogen test.

We agree with Dr Blaisdell that the use of standardized low doses of heparin while practical in the case of patients undergoing a routine operative procedure such as hip surgery, is not reliable in patients who may be suffering from severe trauma, sepsis, shock, or multiple organ failure. Perhaps what

is needed now are trials in which the dose of heparin is adjusted for each patient to a standard end point (mean plasma heparin concentration or activity). In seriously ill patients the use of relatively noninvasive techniques such as the ^{125}I fibrinogen test and the bedside isotope venogram would be essential.

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Advances in the Management of Clinical Heart Disease vols II and III. Edited by Jacob I. Haft, M.D. and Charles P. Bailey, M.D. Mount Kisco, N.Y. 1978. Futura Publishing Company. Vol. II 308 pages. Vol. III 280 pages. Price each volume \$19.75.

These two volumes represent the proceedings of the Second Saint Michael's Medical Center Cardiology Symposium on *Advances in the Management of Clinical Heart Disease*. Volume II is concerned primarily with coronary heart disease viz. myocardial infarction and angina pectoris. The surgical and medical managements are discussed, but this reviewer finds it difficult to understand the data and recommendations especially as related to the surgical results and recommendations. For example, on page 298, the reference to Mullen and associates, it is stated "there were no survivors in this series of 60 patients who had a low preoperative cardiac index and absent septal motion judged by the left anterior oblique ventriculogram. Despite these observations their operative and late mortality was only 33 and 83% respectively." Therefore, what are late results? What about the interpretation of this statement? The ordinary practicing family doctor will find this volume to be useful and the cardiologist who follows the literature already has his information and plans in practice.

Volume III is concerned with three aspects of cardiovascular disease, namely: therapeutics, hypertension and echocardiography. There are rather brief discussions of the management of arrhythmias, cardiac pacing, dissecting aneurysms of the aorta, valve surgery, sensitivity to cardiac glycosides and hypertension and the use of echocardiography in the evaluation of valvular heart disease. These presentations are intended for the practicing physician but are at the level of cardiologists to a major extent, such as the use of cardiac pacing and echocardiography. The family physician will learn of the recommendations and practices of the contributing authors. The discussions are not presented critically for the benefit of the readers who are fully trained cardiologists. These two volumes are of some interest but are not outstanding.

Clinical Nuclear Cardiology. Edited by Robert W. Parkey, M.D., Frederick J. Bonte, M.D., L. Maximilian Buja, M.D. and James T. Willerson, M.D. New York 1978. Appleton-Century-Crofts, Inc. 338 pages. Price \$38.50.

This book describes a new subspecialty of nuclear medicine and of cardiology. But is its value in clinical medicine yet established? The many contributors to this book review the field for clinicians rather thoroughly. The editors of the publication fail to indicate established indications for the use of radioactive elements and nuclear medicine in cardiology. The contributors do present adequately what is now the practice. There is a need to know, for example, whether or not direct intracoronary injection of a nuclide justifies the cost and risk. Furthermore, it is yet to be shown that the information sought is derived or even equal to that obtained by the well established clinical procedures. Those who record electrocardiograms properly and can interpret them surely do not need myocardial imaging to detect, locate and learn the size of an infarct of the myocardium. Regardless, the book in 15 chapters, reviews the field well. The illustrations are good and the subject is discussed so that the reader will learn applications of nuclear medicine to cardiology.

Advances in Cardiology: Sudden Coronary Death. Vol. 25. Edited by Vesa Manninen and Pentti I. Halonen. Basel, Switzerland 1978. S. Karger AG Medical and Scientific Publishers. 231 pages. Price \$77.00.

This is another excellent volume of *Advances in Cardiology*. It contains interesting and important discussions. For example, physical activity and sudden death, life changes and sudden death, cardiomyopathy and sudden death, neural influence and sudden death, the role of the coronary ambulance and sudden death and the coronary care unit and sudden death are among the discussions. This is a valuable book which is easy to read and is concerned with an important problem: sudden death. The book should interest all doctors.

Books received

Coronary Care. By Norman L. Goodland. Chicago 1978. Year Book Medical Publishers, Inc. 88 pages.

Developments in Cardiovascular Medicine. Edited by C. J. Dickinson and J. Marks. Baltimore 1978. University Park Press. 371 pages. Price \$74.50.

The New American Medicine Show. By Dr. Irving Oyle. Santa Cruz, California 1979. Unity Press. 110 pages. Price \$5.95.

Song of Life. By Sushil K. Gupta. Milton, Mass. 1979. Sverge Haus Publishers, 39 pages.

Computerized Tomography in Clinical Medicine. By Patricia Davison Laffey, M.D., Wilbur W. Oaks, M.D., R. Kumar Swami, M.D., J. George Teplick, M.D. and Marvin E. Haskin, M.D. Philadelphia 1978. Medical Directions, Inc. 57 pages. Price \$16.00.

Mechanisms of Hemostasis and Thrombosis. Edited by C. Harold Mielke, Jr., M.D., F.A.C.S. and Robert Rodeviken, M.D. Associate Editor. Chicago 1978. Year Book Medical Publishers, Inc. 302 pages. Price \$29.95.

into displacement activity keeps them too busy to deal with the business in hand—which should be preparing to go back to their lives as winners instead of losers. The physician's urging them to stay out of bed and return to work quickly colludes with their morbid desire to die rather than submit to enforced quietude. Deprived of room for maneuver¹¹ and having learned nothing from the experience of breaking down they may hasten back to the same old problems with the same old tactics and break down again and again at five times the rate of their more passive (Type B) brethren who may have been overcome by chronic overloading at work serious life dissatisfaction bereavement helplessness sleeping difficulties domestic disharmony and attempts to adapt or habituate to life changes which only stripped their strength and coping ability^{12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100}. It is easy to suppose that the ability to resist a coronary breakdown diminishes as the coronary arterial abnormalities increase but we know that it can take place irrespective of the severity of the coronary arteriographic picture² and many people with severe arterial abnormalities appear to lead vigorous lives and support heavy burdens without breaking down their health by forcing storms of excessive demands upon their coronary circulation.

In Schumacher's exercise we should put it down on the maps that few of the unfortunate maintain intact homeostasis before the breakdown.

Most of them have arrived at angina acute coronary insufficiency myocardial infarction or sudden death after a long period of exhaustion¹. This itself causes disability because the heart rate rises excessively in response to physical and emotional challenges and the blood pressure climbs too high for too long in response to common or garden stimuli. Relatively small amounts of exercise produce the symptoms previously associated with severe effort and the coping ability is much reduced in these subjects who are played out by continuous work disturbed sleep and continuous strain or exhausted by constant strain day and night affected by sleeplessness unable to go away and leave their posts. It is now accepted that profound abnormalities of the blood lipids sugar ure acid and coagulability and defects of many other systems are likely to result from severe and prolonged struggles^{2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100}.

It is not known how exhaustion produces this condition of sympathoadrenal hyperactivity and instability^{12, 13} where homeostasis has such a weak grasp of the internal milieu but it does seem to underlie most cases of paroxysmal arrhythmias angina pectoris acute coronary insufficiency arrhythmia hypertension and common sense dictates the need to reverse it before good health can be recovered. If we fail to reverse it we may be tempted to adopt symptomatic remedies such as long term beta blockade or even open heart surgery if arteriography happens to show seductive coronary arterial narrowings.

On my map it would be shown prominently that the unfortunates who suffer a coronary breakdown in health have certain basic needs. They require adequate rest¹¹ and good sleep¹² to overcome exhaustion and defeat and to recover a stronger homeostasis it can still be taken as axiomatic that if the patient does not get sufficient sleep he will never get well. They need the support of warm and close human protection during their period of helpless dependence and adequate relief of pain anxiety and despair¹. They need time and room for maneuver to work out where they went wrong and to choose fresh tactics for the future¹¹. Usually they need a commanding influence to keep them out of the battle for long enough to get well. Above all they need to be trained to get fit enough and tough enough to go back to their lives as winners, avoiding the old self-destructive patterns of behavior which may have been derived from a defective social education from loneliness perhaps from growing up in a footloose society or from life in an area of recent emergence from poverty. Most need to improve their ability to deal with time pressures¹ and information input overloading¹¹. Many have to be shown that they need not despair of becoming well merely because Aesculapians have failed to cure them with the drugs and operations which happen to be fashionable at the time¹.

Aesculapians whose maps do not show these basic needs prominently may be ignorant of the arrhythmic hazards of emotional arousal¹ and the intrarrhythmic importance of sleep¹² and so they may increase the hazards of myocardial infarction by putting people into depersonalised intensive care units amongst frightening technological paraphernalia. They may compare the effects of one

Editorial

The responsibility of the cardiologist mapmaker

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The task of the philosopher is to provide a map of life and knowledge which exhibits the most important features of life in their proper prominence

E F Schumacher 1977¹

E F Schumacher suggests that the last three centuries of aggressive scientific imperialism have given us bewildering maps which omit most of the features that really matter because the mapmakers have concentrated on things which allegedly could be proven their first principle was If in doubt leave it out Since the question of what constitutes proof is subtle and difficult Schumacher recommends the exercise of turning the principle into its opposite and saying If in doubt show it prominently This exercise is useful to the cardiologist because his clinical duties oblige him to deal with large and important features which cannot yet be measured (unless he restricts his life to the laboratory) and as a mapmaker for patients and students he cannot evade his obligations to point out the routes of choice

In the coronary field the first step in the exercise must be for the cardiologist to decide whether he is an Aesculapian godsent to cure the disease or a disciple of Hygeia believing that his main responsibility is to find out where

the patient's life went wrong and teach him how to get back on the good health which was his birthright After half a century of neglect it looks as though Hygeia may come into her own again because doctors who can enter into their patients lives are still insisting that behavior and circumstances can have profound effects upon the cardiovascular system and science is providing increasing support for their opinions by revealing the morbid effects of some aspects of life experience in susceptible persons

In this exercise our maps should show quite plainly that many coronary patients have a behavior problem and the younger they suffer the coronary breakdown the more serious the problem is likely to be Most of them are strivers and achievers restlessly addicted to work and tension guilty when wasting a minute enjoying the attack but never gratified by achievement (Type A) and capable of driving themselves far beyond the range of their homeostasis ability to maintain a normal internal milieu^{2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100} The coronary breakdown is often their comeuppance occurring either when they allow themselves to suffer defeat at the hands of others or when they defeat themselves by running out of time or strength^{1,2} There are a number of good reasons why they consistently conceal this from the interrogator the burdens of explanation are too great³ denial moves in to conceal their inadequacies from themselves and others^{4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100} arrhythmic and self destructive life styles are presented as normal and the psychological need for escape

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Schumacher exercise of showing prominently the features which many omit from their maps because they regard them as in doubt unmeasured and unproved. The emotional reaction of the reader is more likely to depend upon his philosophy than upon the measured and proved needs of his patients. Is this as it should be?

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antiarrhythmic drug with another and never state whether their acute care units help the recovery of homeostasis or incubate sudden death. After the acute phase of the illness they may provide a relatively inflexible program of activity¹ which scarcely fits any particular patient because they think of themselves as dealing with a disease and not as serving people with infinitely variable coping abilities and circumstances.

These Aesculapians can make extraordinary errors with patients suffering from angina pectoris because their maps do not show that the majority will get well if they follow the ancient rules of taking care to sleep well to avoid exhaustion and above all to avoid producing angina^{2,4,8,21,8} each attack of which overdistends the left ventricle and creates the risk of replacement fibrosis or fatal arrhythmia.³¹ Instead of being given the ancient rules the patient is likely to be given a map which overemphasizes risk factors of dubious value.³² Far from attending to the basic needs and encouraging obedience to the ancient rules the Aesculapian may create drug trials in which the patient is actually encouraged to produce pain in his daily life and invited to keep a trinitrin count.³ And once again the published trials compare one drug with another but not with the effect of taking care of the basic needs and following the ancient rules.

If the angina worsens because the patient is not taught how to get well the Aesculapian assumes that the disease has got worse escalates the investigations and therapy and begins to discuss the implications of surgical treatment. This approach may increase the anxiety and the relative coronary insufficiency and precipitate a breakdown—a tragedy if all the patient really needs is the removal of exhaustion and hyperarousal and the provision of good sleep to enable the demands upon the heart to fall back within the frame of coronary competence.³

An important feature of the cardiologist's map has always been iatrogenic disorder and in my opinion this has been expanded beyond belief by the beta blockers. It is now commonplace to encounter the expected and reversible complications of reduced cardiac output such as cerebral vascular insufficiency intermittent claudication weakness tiredness and inability to cope with tasks and a frequent cause of consultation is the patient's inability to convince his doctor that the

beta blocker is doing nothing to halt his deterioration towards a second or third myocardial infarction. In some cases the doctor thought the drug effects were caused by arteriosclerotic deterioration. In other cases he has recognized the noxious effects of his therapy but the propaganda has made him fear to stop it. All too often the doctor was so persuaded of his drug's virtues that he closed his mind to his patients' heretical reports.³⁴

It is time someone put on the map the belief that it might not be dangerous to stop beta blockade provided that sleep deprivation exhaustion and morbid arousal have been dealt with first.³ I regard it as essential to stop beta blockers during my preparation of a cardiac patient for training at the gymnasium. Beta blockers may increase effort capacity by 25 to 50% in angina pectoris³⁵ which is negligible by our standards but they fail to prevent the left ventricular end diastolic pressure from rising too high with exercise.³⁶ It is this excessive rise of pressure which increases the left ventricular wall tension creates patchy ischemia and invites arrhythmia and sudden death and which also stiffens the pulmonary venous system thereby creating unpleasant dyspnea instead of pain in some cases. Furthermore beta blockade restricts the freedom of the heart rate to rise and so removes our simplest guide to the net effect of exercise fatigue and emotional arousal during cardiac rehabilitation.

Coronary artery bypass grafting must have a place on the cardiologist's map because it exists so widely and profitably and because it has such a large industry growing up about it. It is a pity that the evaluation has been so poor³⁷ because its logic is unappealing. Some people generate angina get over their troubles and recover. Others keep it going for years aggravate it at will and crash into infarction and sudden death almost regardless of the appearances of the coronary arteries and myocardium when they begin their careers of ill health pain and disability.³ The operation may bypass some of the debris and damage accumulated during their arteriopathic catecholamine storms but how can it teach them to survive? It is surprising how uncommonly surgical treatment is sought when a strong and humane attempt has been made to meet the basic needs and to teach the ancient rules of angina.

This editorial is one cardiologist's attempt at

Early diagnosis of pericarditis in acute myocardial infarction

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Although pericarditis developing during the acute phase of myocardial infarction has not been shown to substantially increase the hospital mortality rate^{1,2} recognition of this complication remains important in order to avoid other diagnostic possibilities including extension of the infarction and extensive myocardial damage based on the elevation of the ST segment.³

The purpose of this study is to explore the predictive value of several factors in the patient's profile that can alert the physician to the early diagnosis of pericarditis in acute myocardial infarction. The value of salicylate treatment is also assessed in these patients with a review of the literature.

Materials and methods

Data on all patients admitted to the Coronary Care Unit of the American University Hospital between July 1 1977 and December 31 1978 were stored on a system 3 digital computer. Two hundred and sixty one patients had unequivocal evidence of acute myocardial infarction based on at least two of the following criteria: (1) typical history of prolonged coronary pain (2) evolution of ST-T wave changes and abnormal Q waves and (3) significant rise in serum enzymes creatine phosphokinase (CPK) as determined by the method of Okinaka and associates glutamic oxaloacetic transaminase (GOT) and lactic dehy-

drogenase (LDH) frequently with isoenzyme determinations. Patients were continuously monitored between 3 and 5 days and on subsequent days when major complications developed. A 12 lead electrocardiogram was recorded daily 3 days on all patients and daily thereafter if pericarditis or other major complications occurred. A portable chest x-ray was done on admission and was repeated at least once during the hospital stay. Serum enzymes were determined on admission and for 3 consecutive days. Subsequent determinations were done if extension of infarction was suspected or when pericarditis developed. The patient's demographic clinical characteristics coded and stored in computer included the following: age sex quality of pain on admission previous history of coronary pain location of the infarction previous documented myocardial infarction and delay of admission to the hospital in hours. Complications previously established to occur in acute myocardial infarction were also identified. Individual arrhythmias are classified according to Chou and ventricular arrhythmias were graded according to a modification of Lown and associates.⁴ Primary ventricular fibrillation was diagnosed when the arrhythmia occurred within 48 hours from admission and secondary ventricular fibrillation was diagnosed when this arrhythmia occurred in the setting of pump failure after 48 hours. Fascicular blocks were diagnosed according to the criteria of Rosenbaum and colleagues.⁵ Heart failure was classified according to the criteria of Killip and Kimball.^{6,7} Blood lipid abnormalities were classified according to Fredrickson.⁸ Other stored information included: intake established coronary heart disease

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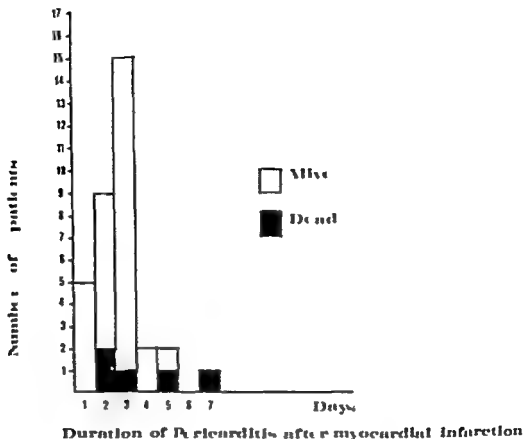


Fig 2 Duration of pericarditis after myocardial infarction

$$Y = a + b_1X_1 + b_2X_2 + \dots + b_nX_n$$

Where Y is the dichotomous dependent variable indicating the presence or absence of pericarditis the b 's are the regression coefficients. The X 's are the independent variables, and a is the constant.

Using such a technique it was possible to calculate for each of the variables the proportion of the variation explained by the factor under consideration.

Results

Clinical characteristics and risk factors Of the 261 patients with acute myocardial infarction 38 with transmural myocardial infarction had pericarditis (14.5%). All patients were males. Some of the clinical features are shown in Table I. A comparison between the pericarditis patients and their controls did not reveal any significant difference as to the character of chest pain on admission, history of previous myocardial infarction or angina, or the location of infarction. A confirmatory two-component friction rub was audible in all patients; this occurred between the second and fourth day from the onset of myocardial infarction.

pain in 33 patients. In none of the patients did friction rub appear after the fifth day (Fig 1). In the majority of the patients who died the pericarditis lasted longer than 3 days (Fig 2).

Considering that the pericarditis in these patients was caused by the pathological process related to the myocardial infarction, the time period between the onset of symptoms of myocardial infarction and the onset of pericarditis was calculated as an expression of the incubation period of pericarditis. Using the method of S. L. Lichstein¹ as applied to non-infectious diseases, the median incubation period and its dispersion factor were calculated for pericarditis following myocardial infarction based on our own data and on data from Lichstein and co-workers.¹ The estimated median incubation period was 42 hours with a dispersion factor of 1.53. Thus about 95% of the pericarditis is expected to develop between 1 and 95 hours from the onset of the myocardial infarction.

Twenty-nine pericarditis patients had congestive heart failure Killip's class II or above compared to 15 matched controls. This difference was statistically significant (Table II). Radiological

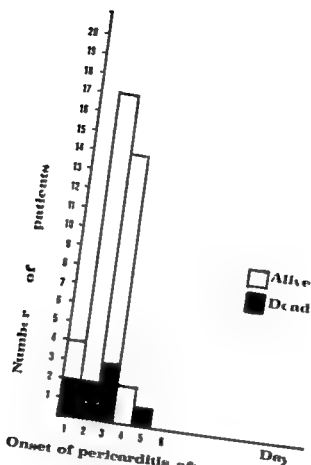


Fig 1 Onset of pericarditis after myocardial infarction

factors, hospital stay in days and mortality status. A detailed problem oriented medical record was constructed on each patient which permitted accurate and frequent documentation of events. No postmortem studies were done.

The diagnosis of pericarditis (AMI P) was made when a two component friction rub was heard by the house staff and was confirmed by at least one senior cardiologist. Those who developed a friction rub after cardiopulmonary resuscitation were not included in the study. Patients with pericarditis and controls were examined several times a day.

Each case of pericarditis (AMI P) was matched with one control of the same age and sex from the remaining 223 patients with acute myocardial infarction but with no evidence of pericarditis. Thus 38 controls (AMI C₁) were selected at random either from the dates preceding or following the date of admission of the case of pericarditis.

As an initial step in analyzing the data comparisons were made between the cases of pericarditis and the remaining group of acute myocardial infarction patients with no pericarditis (AMI C₂) in addition to the case control comparisons between AMI P and AMI C₁. The percentage distributions of cases and controls were calculated for each characteristic and a matched pair analysis was done for the comparison of AMI P and AMI C₁. Such comparisons were used to assess variables that could have a predictive value in identifying patients admitted to the coronary care unit who are at risk of developing pericarditis as a complication of acute myocardial infarction.

In addition using the Statistical Package for the Social Sciences Program, a stepwise multiple regression analysis was done. In order to develop a predictive model for pericarditis in acute myocardial infarction the effect of significant independent variables was assessed in a stepwise manner adding one variable at a time. Thus the predictive value of each of these variables could be assessed following adjustment for the rest of variables. The model used was

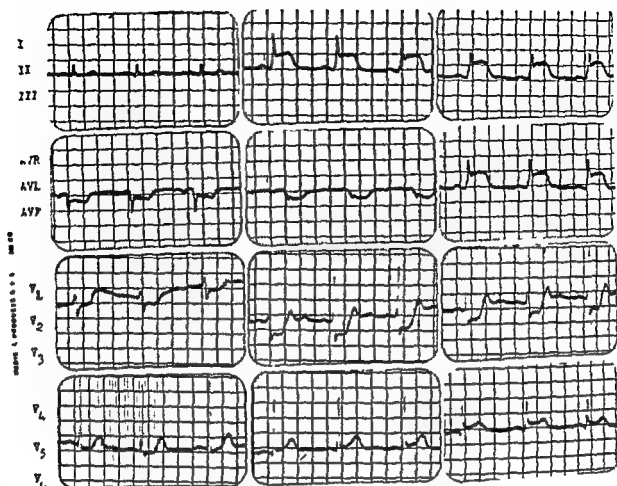


Fig 3 Twelve lead electrocardiogram showing acute inferior myocardial infarction with reciprocal change

Table III Percent frequency of complications in pericarditis and controls

| | AMI P | AMI C ₁ | AMI C ₂ |
|------------------------------|-------|--------------------|--------------------|
| Cardiomegaly | 21 | 18 | 17 |
| S gallop | 21 | 10 | 7 |
| Papillary muscle dysfunction | 15 | 5 | ~ |
| Cardiac arrest | 13 | 3 | 11 |
| Pneumonia | 13 | 10 | 7 |
| Extension of infarction | 5 | 5 | 3 |
| None | 0 | 34 | 33 |

Table IV Peak serum enzyme levels in patients with pericarditis and their matched controls

| Enzyme | AMI P (mean \pm SD) | AMI C ₁ (Mean \pm SD) | t | P |
|--------|--------------------------|---------------------------------------|------|--------|
| CPK | 50.4 \pm 27.1 | 31.6 \pm 23.3 | 2.20 | < 0.05 |
| LDH | 1863.9 \pm 847.1 | 1743.5 \pm 732.7 | 2.66 | < 0.05 |
| SGOT | 123.7 \pm 67.4 | 94.6 \pm 107.8 | 1.62 | NS |

Mortality Eight (21%) of the pericarditis patients died in the hospital compared to 5% in matched control AMI C₁ ($P < 0.01$). The total mortality rate of all the myocardial infarction patients without pericarditis was 17% and difference was not significant compared to pericarditis patients (Table VI).

Discussion

Pericarditis in myocardial infarction has clinically recognized to occur between 6.6% to 16% in various series^{1,2,3} while in an autopsy series 80% of patients with myocardial infarction had pericardial involvement.⁴ This discrepancy might be attributed to (1) inadequate documentation in clinical retrospective studies (2) the fulminating nature of the diagnostic pericardial friction rub and (3) the lack of predictive factors alert the coronary care staff to the patient at risk of developing pericarditis.

The higher incidence of pericarditis in our study compared to other clinical studies (Table

evidence of congestive heart failure included pulmonary congestion (10 patients) acute lung edema (three patients) and cardiomegaly (two patients). In addition six pericarditis patients had a combination of infiltrates atelectasis or pleural effusion. Seventeen patients had normal chest x rays.

In six patients diffuse ST segment elevation typical of pericardial inflammation was noted at the time pericarditis was diagnosed clinically (Figs 3 and 4). In the rest of the patients the appearance of the rub was not associated with any significant ST shifts. In patients with anterior infarction the peak ST elevation measured within 24 hours from onset was 5.9 mm for AMI P compared to 2.8 mm in AMI C₁ ($P < 0.01$). For patients with inferior infarction these averages were 2.9 and 2.2 mm respectively ($P < 0.05$).

All patients with pericarditis had one or more complications of myocardial infarction while at least one third of the controls were free of complications (Table III). Twenty four pericarditis patients had sinus tachycardia compared to 13 of the matched controls. There was no difference in the occurrence of supraventricular or ventricular arrhythmia, atrioventricular or fascicular blocks. The two groups did not differ significantly as to the presence of the following risk factors: diabetes, hyperlipidemia, hypertension, smoking, positive family history of coronary heart disease, hyperurcemia and obesity.

Laboratory results. Pericarditis patients had significantly higher mean values of peak CPK and LDH compared to the matched controls ($P < 0.05$) as shown in Table IV. SGOT peak values did not show such a difference. Six out of eight pericarditis patients who died had CPK values higher than 60 while only five of the 30 surviving had such high values of CPK ($P < 0.01$).

Multiple regression analysis. In an effort to assess the predictive value of these clinical and laboratory findings for pericarditis in acute myocardial infarction a stepwise multiple regression analysis was done using the presence or absence of pericarditis as the dependent variable and the Killip classification for congestive heart failure, the peak ST segment elevation in millimeters within 24 hours from onset and the peak values for LDH, CPK and SGOT as the independent variables. As illustrated in Table V following

Table I Clinical characteristics of patients with pericarditis (AMI P) and matched controls (AMI C₁)

| | AMI P (No) | AMI C ₁ (No) | Total MI (No) |
|-------------------------------------|----------------|----------------------------|------------------|
| Total patients | 38 | 38 | 261 |
| Previous MI | 8 | 7 | 100 |
| History of angina | 22 | 23 | 155 |
| Typical pain on admission | 36 | 31 | 217 |
| Location of MI | | | |
| Anterior | 24 | 21 | 118 |
| Inferior | 12 | 12 | 97 |
| Mixed | 2 | 1 | 46 |
| Hospital mortality | 8 | 2 | 46 |
| Admission to hospital within 6 hr | 24 | 22 | 155 |
| Mean age \pm SD (days) | 58 \pm 10.33 | 58 \pm 10.28 | 57.6 \pm 11.90 |
| Mean length of stay \pm SD (days) | 10.4 \pm 5.5 | 11.6 \pm 7.9 | 10.3 \pm 6.0 |

Table II Killip's classification of heart failure in AMI P and AMI C₁

| | Killip's Class | | | | |
|--------------|----------------|----|-----|----|-------|
| | I | II | III | IV | Total |
| Pericarditis | 9 | 22 | 1 | 1 | 38 |
| Controls | 23 | 9 | 5 | 1 | 38 |

$$\chi^2 = 11.66 \text{ df} = 3 \text{ } P < 0.01$$

multiple adjustment the variable that could explain more of the variation as to the development of pericarditis was the ST segment elevation and a significant contribution by this variable was maintained throughout the stepwise multiple regression analysis. The regression coefficients for the peak enzyme values and the Killip classification for congestive heart failure were small and not significant and were of minimal predictive value.

Treatment. Thirty one patients were treated with salicylates at an average dose of 2 to 3 grams per day for 10 to 14 days. Response was satisfactory in 27 patients (87%) with prompt and sustained relief of pain without complications. Follow up at 3 weeks following discharge did not show recurrence of pericarditis or the development of post myocardial infarction syndrome.

Table VI Percent mortality in pericarditis and controls after MI in various series

| Series | Total number of pericarditis patients | Death in pericarditis | | Death in controls (%) |
|-----------------|---------------------------------------|-----------------------|----|-----------------------|
| | | No | % | |
| Thadani et al | 52 | 10 | 19 | 13 |
| Toole et al | 40 | 8 | 20 | 12 |
| Niarcho et al | 27 | 4 | 18 | 12 |
| Barman et al | 106 | 18 | 17 | 10 |
| Lichstein et al | 31 | 3 | 10 | 12 |
| Liem et al | 41 | 2 | 5 | 7 |
| Guillemin et al | 61 | — | 2 | 9 |
| Present series | 38 | 8 | 21 | 5-17† |

Mortality in age and sex matched controls

†Mortality in all patients with acute MI without pericarditis.

Table VII Clinical incidence of pericarditis complicating MI*

| Series | Total MI | Pericarditis | Incidence (%) |
|-----------------|----------|--------------|---------------|
| Thadani et al | 739 | 52 | 7.8 |
| Toole et al | 551 | 40 | 7.2 |
| Niarcho et al | 193 | 27 | 11.3 |
| Barman et al | 1284 | 106 | 8.3 |
| Lichstein et al | 70 | 31 | 10.1 |
| Liem et al | 300 | 44 | 14.7 |
| Guillemin et al | 400 | 61 | 16.0 |
| Present series | 261 | 38 | 14.5 |
| Cumulative | 4078 | 397 | 11.1 |

MI myocardial infarction

mapping studies and the standard six lead precordial electrocardiogram⁴ improves the value of the latter tool in the diagnosis of pericarditis.

Sinus node and atrial irritation described by James⁵ in patients with pericarditis increase the vulnerability to supraventricular arrhythmias.⁶ Arrhythmias are rather common complications in myocardial infarction.^{4,7} Most studies^{2,4,8} unlike ours have indicated a high incidence of arrhythmia in patients with pericarditis.

Our findings of increased pump dysfunction in patients with pericarditis are in agreement with previous observations. This dysfunction is a reflection of increased myocardial damage in these patients manifested by the pericardial involvement.¹ The appearance of the pericardial rub within a few hours from the onset of myocardial infarction probably carries a grave prognosis.

It is important to note that in the multiple linear regression analysis the variable that could explain more of the variation as to the development of pericarditis was the ST segment elevation. The finding that the extent of CPH, LDH and SGOT elevation and degree of pump dysfunction did not contribute significantly to explain the variation in this model may be due to the fact that ST segment elevation has measured the same myocardial changes that are expressed by enzyme elevations and pump dysfunction. Thus, ST segment elevation in itself is possibly a better clinical indicator of these changes under these circumstances. Only 35% of the variation could be explained between pericarditis patients and their controls using the above mentioned variables. Further studies need to be done to investigate the possible role of other variables and indicators in this condition.

Summary

Pericarditis complicating acute myocardial infarction assumes increasing importance in this era of quantitating infarct size by precordial ST segment mapping. Early recognition of this complication avoids diagnostic and therapeutic errors. In this study we looked for factors that could alert to the early diagnosis of pericarditis such as ST elevation measured within 24 hours from onset, extent of CPH, LDH and SGOT elevation as well as degree of pump dysfunction. ST segment elevation in millimeters on admission seemed to be one factor that was of predictive value in this condition.

Pericarditis occurred in three forms: (1) within a few hours from the onset of myocardial infarction and this form seems to carry a high mortality rate; (2) a more common variety occurs within 24 to 72 hours from onset and carries a higher mortality rate than matched controls; and (3) the late syndrome of Dressler's, not observed in our series. Aside from increased incidence of heart failure, other complications of myocardial infarction and the coronary risk factors were not significantly higher in patients with pericarditis. Salicylate treatment offers immediate relief in the majority of patients.

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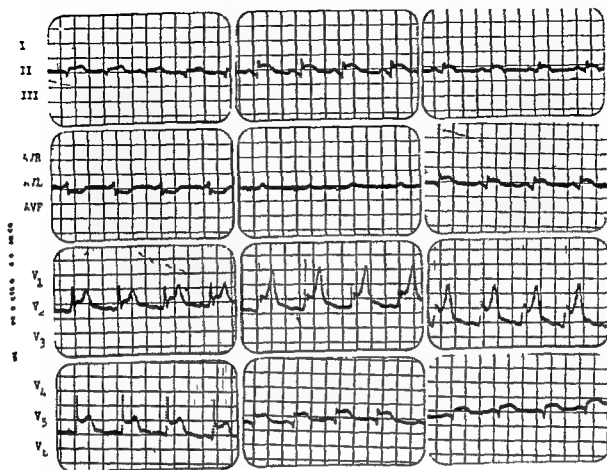


Fig 4 Electrocardiogram (in the same patient as in Fig 3) 72 hours later showing diffuse ST-T wave changes of pericarditis

may in part reflect the prospective nature of the study similar to the findings of Liem and colleagues and Guillemin and Valere.² This increased yield may also be due to the heavy staffing of our Coronary Care Unit. As in other studies, the friction rub appeared between the second and fourth day in the majority of patients. In two patients the friction rub appeared within 4 hours from the onset of myocardial infarction and both of these patients died. The early appearance of the rub in these patients probably reflects more extensive myocardial damage. Five out of six patients whose rub persisted beyond 3 days died. This tendency was also noted in other studies.¹ There was no recurrence of the rub or appearance of Dressler's syndrome at 3 weeks following discharge, an encounter noted by Niarcho and McKendrick but at variance with earlier reports.¹ The findings of high CPK and LDH values in the pericarditis patients are in agreement with those of Thadani and colleagues.¹ The extent of myocardial cell damage has been

Table V Results of multiple linear regression analysis

| Variable | b | SEb | P | Percent of variation explained |
|----------------|--------|--------|---------|--------------------------------|
| ST elevation | 0.1062 | 0.0273 | < 0.001 | 37.0 |
| Peak LDH | 0.0001 | 0.0001 | N.S. | 1.4 |
| Killip's Class | 0.006 | 0.0665 | N.S. | 1.0 |
| Peak SGOT | 0.0006 | 0.0006 | N.S. | 0.9 |
| Peak CPK | 0.0009 | 0.0078 | N.S. | 0.1 |
| Constant | 0.0739 | | | |

correlated with the magnitude of ST segment elevation.¹⁰ Lichstein⁹ reported more marked ST segment shifts in their patients with pericarditis. Hardarson and co-workers⁶ and Zmyslinski and colleagues¹¹ noted a secondary rise of persistent ST elevation in the patients who developed pericarditis studied by precordial mapping. The good correlation demonstrated between precordial ST

Evaluation of the anatomy of congenitally malformed aortic valves by orifice view aortography

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Employing a cine aortographic technique whereby the patient is rotated so as to cause en face viewing of the aortic valve, it is possible to determine aortic valve area accurately. This technique of orifice view aortography is particularly useful in children where the assessment of aortic stenosis often necessary prior to the development of symptoms is at times difficult and occasionally not possible by conventional means. Of considerable importance in such individuals may be knowledge of aortic valve anatomy especially as it pertains to operability by simple valvular commissurotomy as opposed to aortic valve replacement.

This study presents the results of a critical review of our experience using this technique with congenital aortic valvular malformations in regards to the ability to delineate accurately the appearance of the aortic valve.

Materials and methods

Nineteen patients with clinical findings indicative of congenital aortic valve malformations were studied. The age of the patients ranged from 11 to 36 years average 19 years. The technique and method of photographing the aortic valve en face has been previously described in detail and

the technique for positioning the U arm angiographic system to achieve this view has also been described. Briefly the patient is positioned on the angiographic table in the direct right lateral projection and the table is angulated 35 to 40 degrees off the vertical causing the x ray beam to travel essentially from the right axilla to the left iliac crest. Aortography is then performed with a standard catheterization technique the tip of the catheter being positioned in either sinus of Valsalva. The aortic valve is thus viewed as though looking into the aorta as it exits the heart. The orientation of the valve on the film is such that the right and left aspects are respectively to the viewer's right and left the superior and inferior aspects respectively represent the anatomic anterior and posterior aspects.

The congenitally abnormal aortic valves were all viewed in this manner and were analyzed for configuration including the number of commissures and thus the number of functioning leaflets, the appearance and position of each leaflet, the presence or absence of an identifiable leaflet raphe, the appearance and position of the valve orifice and the number as well as sinus of origin of the coronary arteries. Each was also analyzed for the presence of aortic regurgitation without consideration to degree. In addition the area of each valve leaflet was planimetrically determined and expressed as a ratio of the larger to the smaller leaflet regardless of their relative positions.

Thirteen patients had clinical and hemodynamic evidence of congenital valvular aortic stenosis with or without associated regurgitation as their only identifiable abnormality. The remaining six patients had other associated malformations of the heart including four individuals with coarctation of the aorta and one each with fixed

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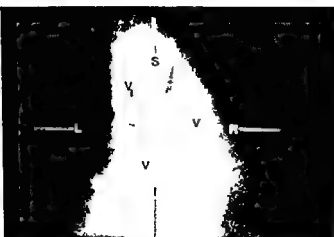


Fig 1 Orifice view of normal aortic valve. Quadrant markers S / R and L indicate superior inferior right and left aspects of angiogram as viewed in this and all subsequent illustrations. All three sinuses of Valsalva (V_1 = left V_2 = right V_3 = non-coronary) are clearly seen densely opacified surrounding the triangular appearing orifice and separated from each other by their respective commissures.

Table II Classification and findings

| | | |
|---------|--|---------|
| Group 1 | Two unequal leaflet | |
| a | Larger leaflet inferior to right to left | 2 cases |
| b | Larger leaflet superior to left | 3 cases |
| Group 2 | Two equal leaflets | |
| a | Superior-inferior orientation | 2 cases |
| b | Right-left orientation | 1 case |

ration. The Group 2 patients (Figs 2 and 3) to the contrary, were clearly bicommissural and anatomically and functionally bicuspid. An identifiable notch or indentation of a leaflet which we interpret as a raphe was present only in the Group 1a valves (Fig 3) and was uniformly present in the dominant leaflet appearing as a rudimentary separation of this leaflet into the right and non coronary components. This raphe is to be distinguished from the commissural fusion resulting in the unicommisural appearance described above.

The planimeterized leaflet areas further allowed grouping as described above. The ratio of the dominant to non dominant leaflet in all Group 1 valves exceeded 2:1 and was less than 3:1. The Group 2 ratio never exceeded 1.6:1.

The orifice appearance was determined by valvular configuration. Thus all Group 1 valves exhibited eccentric positions of the orifice. Group

1a cases having a superior and generally leftward position (Fig 3) and the Group 1b cases having an inferior and either slight rightward or leftward orientation (Fig 4). The Group 1b valves also appeared to have more complete development of each commissure, thus appearing more like the Group 2 valves in this respect and this type of bicuspidization has been indicated by Edwards. The Group 2 valves, however, all had centrally located orifices. Group 2a (Fig 2) having a generally horizontal orientation and Group 2b a vertical orientation (Fig 5).

The 13 patients having aortic stenosis, all accompanied by other anomalies comprise all of Group 1 and as well five cases from Group 2. Thus the remaining cases all having additional anomalies had equally bicuspid valves with the exception of the individual with an unequally tricuspid valve.

Aortic regurgitation

Aortic regurgitation, mild in all instances, occurred in four patients in Group 1 whereas only two patients in Group 2 revealed aortic regurgitation. One of these patients also had subaortic aortic stenosis, a lesion commonly associated with valvular regurgitation, and the other had significant calcific aortic valvular deposits. The individual with unequal tricuspid aortic valvular anomaly also exhibited regurgitation.

Coronary arterial pattern

The origins of the coronary arteries could be identified in 18 of the orifice view aortograms and a definite pattern could be established in regard to the various valvular configurations. Thus in each of the Group 1a valves (Fig 3) the coronary arterial origin appeared essentially normal, the left coronary artery arising from the superior and leftward sinus, the right from the rightward aspect of the dominant inferior sinus always to the right of the leaflet raphe. This pattern appeared to indicate that the raphe indeed demarcates the absent commissure between the right and non coronary leaflets. This pattern of coronary origin did not occur in any of the other valves in the other groups although one of the Group 1b valves had a similar appearance, the right coronary artery arising from the right lateral aspect of the sinus of the inferior and non dominant cusp near the commissure and the left coronary ostium appearing at the left lateral

Table 1 Summary of aortic valve findings

| Group | No of patients | Range of peak aortic gradient (average) | Spatial orientation of leaflets* (cases) | Leaflet size ratio dominant/non dominant | Raphe position in dominant leaflet | Number and situs of origin of coronary arteries (cases) | A/R | Orifice location | Other cardiac defects | Surgery |
|-----------|----------------|---|--|--|------------------------------------|---|-----|--------------------|-----------------------|---------|
| 1a | (5) | 42-63 (53) | Sup N (1) Inf D (3) Sup D (1) | 20-26 | Inf L (2) Inf R (3) | 2 (5) Sup-Inf | 2 | Eccentric Superior | 0 | 1 (C) |
| 1b | (3) | 63-70 (67) | Sup D (3) | 20-30 | — | 1 Sup (1) 2 Sup Inf (1) Undetermined (1) | 2 | Eccentric Inferior | 0 | 1 (R) |
| 2a | (9) | 0-10* (30) | Sup (9) | 10-16 | — | 1 Sup (*) 2 Sup (*) | 2 | Central | 0 | 2 (R) |
| 2b | (1) | 17 (1*) | L/R (1) | 1.3 | — | 2 Right Left (1) | 0 | Central | 0 | — |
| Tricuspid | (1) | 6 (6) | Normal Tricu-pid (1) | — | — | 1 Right (1) | 1 | Central | 1 | — |

Abbreviations: a = Sup-Inf = Superior Inferior D = Dominant Non Dominant L = Left R = Right b = where applicable c = less than 1 indicates single origin of both coronary arteries d = AR = aortic regurgitation e = C = commissurotomy f = R = replacement.
Ref. to spatial orientation not anatomic configuration

subvalvular aortic stenosis and double outlet right ventricle. Four patients have been submitted for surgery, one having aortic valvular commissurotomy and three having valve replacement. The appearance of the valve in these individuals is available for comparison with the appearance on the orifice view aortogram.

Results (Table 1)

The appearance of the normal aortic valve on orifice view aortography is pictured (Fig. 1) for orientation. As viewed in this projection the non-coronary leaflet occupies the most inferior position with the left coronary leaflet appearing superior and somewhat leftward and the right coronary leaflet appearing somewhat inferior and principally rightward. The structure of the congenitally malformed valves was readily evaluated due in part to their tendency to produce a domed appearance during systole. This dome seen as a moderately lucent area surrounding the more lucent and often nearly radiopaque orifice provided very satisfactory visualization of the leaflets (Fig. 2) and allowed their measurement by planimetry following image magnification with projection of the selected cine frames.

Gross appearance (Table II)

The congenitally malformed valves with one exception could be grouped according to gross

appearance either as having two leaflets marked by disparate in size (Group 1) or two essentially equal sized leaflets (Group 2). Additionally, each group could be subdivided depending upon the spatial orientation of the leaflets. Group 1a had the configuration in which the larger (dominant) leaflet was inferior to the smaller (non-dominant) leaflet oriented somewhat to the right in two cases and to the left in three (Fig. 3) whereas the three cases comprising Group 1b (Fig. 4) had the dominant leaflet superior and to the left of the non-dominant leaflet. Group 2a (Fig. 2) exhibited a principally superior-inferior leaflet orientation (nine cases) and Group 2b revealed right-left orientation (one case) (Fig. 5). The sole exception to this classification was a patient having the additional abnormality of double outlet right ventricle in whom the aortic valve was unequally tricuspid with essentially normal leaflet orientation.

The Group 1a valves (Fig. 3) were all unicommissural. Each had one short commissure which allowed partial leaflet separation with systole. The other commissure was fused from valve orifice to periphery. Thus valves of this type may also be considered as functionally unicuspid although two leaflets are identifiable. Those in Group 1b (Fig. 4) although similar appeared to have better development of each commissure and thus all tended toward a bicommissural configuration.



Fig 3 Orifice view of Type 1a valve. Tasky aortic gradient 47 mm Hg. The orifice is marked by asterisk and occupies an eccentric position leftward and superior in the valve incidentally demarcating the superior aspect of the valve dome; the inferior margin demarcated by small arrows. One commissure (C_1) clearly opens into the orifice; the other (C_2) is fused for some distance. The two leaflets are obviously of different sizes; the dominant inferior leaflet revealing an indentation representing a raphe (arrow R). Left coronary artery (lca) arises from the superior sinus and right coronary artery (rca) from rightward aspect of the inferior sinus. This valve is considered a type amenable to simple commissurotomy in view of the long fused commissure.

cannot be satisfactorily calculated hemodynamically and a reliable adjunctive measurement in the presence of satisfactory data obtained at the time of left heart catheterization. During collection of this data it has become apparent that the technique also allows acquisition of information concerning aortic valvular anatomy in addition to orifice size which may have bearing on the method of surgical management.

The aortic valvular anatomic findings by orifice view aortography, although similar, are not identical to the gross anatomic features reported by Roberts. A greater percentage of valves seen angiographically had the appearance of being essentially uncommissural. Thus all of the valves included in Group 1a and one from Group 1b had

such a configuration comprising 35% of the total, excluding the single example of stenotic tricuspid valve Roberts reported a somewhat smaller percentage (20%) of this valve type. This difference, however, may be explained by the fact that most of our patients were children or young adults and this form of aortic valvular malformation has been considered to be the only type inherently stenotic as well as obstructive at birth.¹ It should be noted however that four of our patients with no additional cardiovascular malformations had equally bicuspid aortic valve, two requiring surgery as adolescents suggesting possible significant stenosis from infancy contrasting somewhat with the report by Edwards that such valves became stenotic principally with the aging process. Although each of these valves was essentially without commissural fusion, they did not appear to exhibit angiographically the dysplastic appearance reported in this type of valve as a cause of obstruction by Chellum and associates¹¹ and such was also the case in two valves at the time of surgical excision. The other five patients had associated malformation and all had trivial or absent aortic valve gradient.

Clear cut evidence of a leaflet raphe could be observed angiographically only in those valves representative of Group 1a in which the dominant leaflet appeared to represent fusion of the right and non-coronary leaflets although Roberts occasionally found raphes in either or both leaflets regardless of anatomical appearance.

Similarly, the coronary arterial pattern observed angiographically varies from the findings of Roberts in respect to the Group 1 cases but are identical in respect to those in Group 2.

With these differences from the reported anatomic valvular appearance taken into consideration it seems apparent that orifice view aortography is useful in delineating the anatomy of the malformed aortic valve. In four of our patients so far it has quite reliably predicted the anatomy discovered at surgery. At present attention is being concentrated upon the appearance of the commissures as regards the presence or absence of identifiable fusion and extent of fusion.

The importance of a technique allowing determination of aortic valvular anatomy prior to aortic valve surgery is greatest in childhood and early adult life principally as regards identification of valves amenable to commissurotomy as

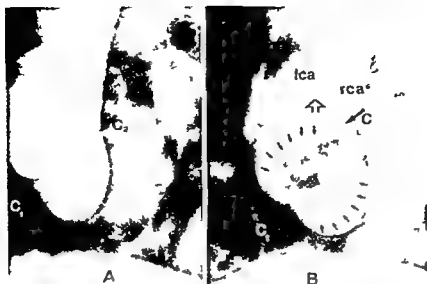


Fig 2 Orifice view of bicuspid aortic valve of Type 2a illustrating features of bicuspidization (see text for description). Peak systolic gradient = 12 mm Hg. Coarctation of aorta is associated malformation. **A** Valve closed. The two commissures are designated by arrows C_1 and C_2 and line of leaflet coaptation may be seen extending from C_2 . **B** Valve open. The commissures are again identified by arrows C_1 and C_2 . The valve orifice presents an elliptical appearance (lucent center) surrounded by a "halo" of lesser lucency (small arrow) which represents the valve dome. The coronary arteries (rca = right, lca = left) are seen to arise from a single vessel (single left coronary artery) from the sinus of Valsalva (open arrow).

aspect of the sinus of the dominant cusp. The other Group 1b valve revealed both coronary arteries to arise from a single ostium and a trunk located at the right lateral margin of the sinus of the superior dominant leaflet. One Group 1b valve could not be analyzed for coronary origin. Somewhat similarly (Fig 2) seven of the Group 2a valves had single origin of both coronary arteries from the sinus of the superior cusp and two exhibited the right and left coronary arteries arising separately, also from the sinus of the superior cusp. The single example of Group 2b had the origin of the right coronary artery from the sinus of the rightward cusp and the left coronary from the sinus of the leftward cusp. Finally, the individual with unequal tricuspid aortic valve had single origin of both coronary arteries from the sinus of the anatomic right cusp.

Anatomic correlation

One patient underwent simple aortic commissurotomy and is the only individual in this series representing Group 1a. The angiographic appearance of the valve in this patient indicated a commissure fused for sufficient length to allow for this type of operation. At surgery, this finding

was confirmed and incision was carried out with out difficulty. The post-operative residual gradient across the aortic valve was 20 mm Hg reduced from 60 mm Hg preoperatively. One individual representing Group 1b with angiographic evidence of a nearly continuous slit like orifice without apparent significant commissural fusion required valve replacement. Likewise two examples of valves having Group 2a configuration with virtually no commissural fusion also required valve replacement. Each of these valves were available in nearly a complete form after surgical removal and each had an appearance similar to the angiographic (Fig 6).

Discussion

The technique of orifice view aortography has been previously shown to be a method by which the size of the aortic orifice could be calculated.² We have recently demonstrated excellent correlation of the aortic valve area measured by orifice view aortography with that calculated by hydraulic equation concentrating on young individuals with congenital malformations of the aortic valve. The sensitivity of the technique is sufficient to allow it to be considered a definitive study for this parameter if for any reason the area



Fig 6 Orifice view of aortic valve Type 2 in left panel and appearance of valve at surgical removal, oriented similarly in right panel. Peak systolic gradient = 102 mm Hg. Dome defined by small arrows with orifice appearing densely lucent within it. Commissures (arrows C_1 , C_2) fused for short distance. Note similar appearance of surgical specimen. Commissures were not fused for sufficient length to allow adequate surgical relief as indicated by aortic angiogram.

opposed to those requiring replacement. If fusion of one or both commissures is observed it is likely that commissurotomy could be performed and provide satisfactory relief of the stenosis. The valves with Group 1a configuration stand out prominently in this respect. On the other hand if the orifice view aortogram shows that there is little or no fusion of the commissures, it is apparent that commissurotomy would not provide satisfactory relief of stenosis and valve replacement would be necessary. Avoidance of prosthetic valves, all types of which currently in use are fraught with the disadvantage of early failure in the essentially symptom-free young patient is preferable to exposing these individuals to the risk of multiple valve replacement and, excepting the porcine xenograft, the potential risk of thromboembolism. Viewing the aortic valve by orifice view projection appears to allow such identification.

Summary

Nineteen patients with congenital abnormalities of the aortic valve were studied by orifice view aortography and the anatomic configuration of each valve was determined. With one exception, all valves were bicuspid. The bicuspid aortic valves could be grouped into two distinct categories. Group 1 valves had unequal leaflet size and could be further subgrouped depending upon the

spatial orientation of the leaflets. The commissural structure of this type of valve was such that, with but two exceptions, valvular configuration appeared essentially unicommissural. The valves comprising Group 2 exhibited essentially equal-sized leaflets and thus are considered equal bicuspid. These valves displayed a central orientation of the orifice and thus are bicommissural, in contrast to the unicommissural Group 1 valves which all had eccentric orifice position. The aortic valves examined by this technique exhibited close similarity to descriptions of valves at the time of pathological examination.

Orifice view aortography appears to be a reproducible method of determining the anatomy of the aortic valve which can be applied as a preoperative evaluation useful in determining whether relief of aortic stenosis by aortic commissurotomy, as opposed to valve replacement, is feasible. Four patients undergoing aortic valve surgery, one with commissurotomy and three with valve replacement, have revealed findings at the time of operation confirmatory of the anatomical configuration of the valve predicted by orifice view aortography.

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Fig 4 Orifice view of aortic valve Type 1b Peak systolic gradient = 63 mm Hg Edge of dome demarcated by small arrows Each commissure (C_1 - C_2) is open for a short distance toward the orifice (arrow 0) The dominant leaflet is oriented superiorly and the non-dominant is oriented inferiorly The single origin of both coronary arteries (rca and lca) is identified by arrow (a) This valve appears amenable to commissurotomy due to the appearance of significant fusion of each commissure



Fig 5 Orifice view of Type 2b aortic valve Contrast with Fig 4 Peak systolic gradient = 17 mm Hg The elliptical centrally placed lucent orifice is vertically oriented in the valve dome identified by opposing solid arrows Commissure C_1 appears non fused whereas C_2 is fused to valve periphery

The clinical importance of cardioselectivity and lipophilicity in beta blockers

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Ever since Lands in 1967 proposed the existence of two types of beta receptor—beta 1 and beta 2—it has been theoretically desirable for a beta blocker to possess the property of cardioselectivity i.e. to preferentially block in a competitive fashion the cardiac beta 1 receptor leaving the peripheral beta 2 receptors relatively unhindered. A beta blocking agent which is non selective might be expected to confer all the benefits of beta 1 blockade (Table I) but possibly be harmful in blocking beta 2 receptors in for instance (a) bronchial muscle causing bronchoconstriction (b) blood vessels causing vasoconstriction or (c) the liver and muscle prolonging hypoglycemia.

Another property of beta blockers the partition coefficient in octanol and water has recently gained prominence. A high partition coefficient is associated with lipophilicity and a low coefficient with hydrophilicity. Lipophilic beta blockers in general (a) tend to be metabolized by the liver and (b) reach all compartments of the body with relative ease. Hydrophilic beta blockers tend (a) to be non metabolized and excreted unchanged by the kidney and (b) reach the deeper compartments of the body such as the brain with relative difficulty.

The properties of a beta blocker in particular the properties of cardioselectivity and lipophilicity

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Table I Distribution of some of the main beta 1 and beta 2 adrenoceptors

| Beta 1 | Beta 2 |
|---|-------------------------|
| Heart | Bronchus |
| Plasma renin activity (kidney) | Peripheral blood vessel |
| Intraocular pressure (aqueous humor production) | Uterus |
| | Insulin (pancreas) |
| | Lactic acid production |
| | Free fatty acids |
| | Glycogenolysis |

ty can be predicted from its molecular structure. Beta blockers possess either an ethanolamine or an oxopropanolamine side chain (Fig 1) the latter generally conferring greater potency. The first beta blockers dichlorisoprenaline (DCI), pronethalol and propranolol (Inderal)* (Fig 1) were non selective. Subsequently cardio-selective oxopropanolamine beta blockers (Fig 2A) were developed which had the common structural feature of an amide (practolol—Eraldin, atenolol—Tenormin, acebutolol—Sectral) or other hydrogen binding function (metoprolol—Lopressor or Betaloc) in the para position of the benzene ring. The amide functions in particular also reduce the lipophilicity of the molecules. Thus atenolol for example is both cardioselective and has low lipophilicity (hydrophilic). That cardioselectivity and hydrophilicity do not necessarily go hand in hand though is shown by the examples of Fig 2B.

Beta blockers as a group of drugs are relatively to other types of antihypertensive and antianginal

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| β -blocker | Log part. coeff octanol/water | Cardioselective | Structure |
|------------------|----------------------------------|-----------------|-----------|
| Sotalol | -0.79 | No | |
| Acebutalol | 1.87 | Yes | |
| Nadolol | 0.71 | No | |
| Pindolol | 1.75 | No | |
| Timolol | 2.10 | No | |
| Metoprolol | 2.15 | Yes | |
| Oxprenolol | 2.18 | No | |
| Alprenolol | 2.61 | No | |

Fig 2B Beta blocker partition coefficient in octanol/water, cardioselectivity and structure

does not change after chronic administration.^{1, 12} Lipophilic beta blockers by contrast tend to have short plasma half-lives. The half-life of propranolol after a single dose is 2 to 3 hours but appears to lengthen a little after chronic administration.¹ This fact is due probably to saturation of the liver enzyme system responsible for the metabolism of propranolol.

Clinical implications The possible clinical implications of the above facts are in the areas of dosage interval and predictability of action. The former is dealt with later. The small between-patient variation in peak blood levels of a hydrophilic drug such as atenolol affords a certain predictability of action which is reflected in the narrow dose range for both hypertension and

angina.^{14, 15} This contrasts with the large variation in peak blood levels of the lipophilic but metabolized beta blockers,¹ necessitating individualisation of dosage. However, even propranolol might well have a much narrower dose range than was suggested by earlier studies.¹⁷

Distribution Within the plasma, beta blockers bind to proteins in varying degrees. The degree of protein binding appears to be independent of the partition coefficient. Thus a hydrophilic compound such as atenolol is poorly protein-bound at about 3%.¹⁸ Propranolol, which is highly lipophilic, is about 90% protein-bound,¹ however metoprolol, which is also lipophilic, is only 10% protein-bound.² Now the volume distribution of beta blockers through the various

| β -blocker | Log part. coeff octanol/water | Cardioselective | Structure |
|---------------------|----------------------------------|-----------------|-----------|
| Dichlorisoprenaline | 3.32 | No | |
| Pronethalol | 3.00 | No | |
| Propranolol | 3.65 | No | |

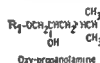


Fig 1 Beta blocker partition coefficient in octanol/water, cardioselectivity and structure

nal agents effective and cause few troublesome side effects. So in practical terms how real are the supposed advantages of cardioselectivity and how relevant is the property of hydrophobicity? The examples used in this paper for cardioselective agents are atenolol and metoprolol and for the non cardioselective agents propranolol (though not exclusively). The representative of the hydrophilic group of beta blockers (practolol, atenolol, sotalol and nadolol) will in the main be atenolol and of the lipophilic beta blockers propranolol and metoprolol. The subject will fall under two main headings:

- 1 Pharmacokinetics highlighting important differences between hydrophilic and lipophilic beta blockers and the clinical implications, and
- 2 Pharmacodynamics of cardioselective and non selective beta blockers and the clinical implications

Pharmacokinetics—contrasting hydrophilic and lipophilic beta blockers

1 Absorption Hydrophilic drugs have difficulty in crossing cellular membranes and tend to be poorly absorbed from the gut. Thus approximately 50% of atenolol¹ and 30% of nadolol are absorbed from the gut. However in the case of atenolol at least at a given dose peak blood levels are relatively constant and predictable, varying only three to fourfold between patients.^{2,3} In contrast lipophilic beta blockers such as pro-

| β -blocker | Log part. coeff octanol/water | Cardioselective | Structure |
|------------------|----------------------------------|-----------------|-----------|
| Atenolol | 0.23 | Yes | |
| Practolol | 0.79 | Yes | |
| Acetabulol | 1.87 | Yes | |
| Metoprolol | 2.15 | Yes | |

Fig 2A Cardioselective beta blockers: partition coefficient in octanol/water and structure

pranolol^{4,5} and metoprolol⁶ are well absorbed though there is some twentyfold variation in peak blood levels. This variability of peak blood levels is presumably due to the fact that these drugs are metabolized by the liver.

Hydrophilic beta blockers tend to have long plasma half-lives. For example the half-life of atenolol after a single dose is 6 to 9 hours^{10,11} and

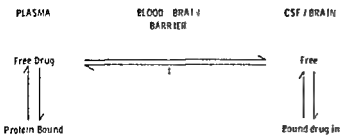


Fig 3 Central nervous system/beta blocker study Beta blocker distribution—blood/cerebrospinal fluid/brain

Table III Accumulation of beta blockers in the lung (dose/mg/kg rat) lung blood concentration ratio (\pm SEM)*

| Beta blocker | Lung blood concentration ratios |
|--------------|---------------------------------|
| Propranolol | 341 \pm 63 |
| Oxprenolol | 185 \pm 11 |
| Metoprolol | 11.5 \pm 0.5 |
| Acebutolol | 54 \pm 0.4 |
| Practolol | 30 \pm 0.1 |
| Atenolol | 19 \pm 0.2 |

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dence of adverse reactions relating to the CNS such as psychosis depression hallucinations nightmares and insomnia.⁶ Psychotic problems and other CNS side effects arising with lipophilic beta blockers which enter the brain in high concentration^{2, 7} disappear or markedly improve when a hydrophilic beta blocker is substituted.^{8, 9} Sixty three such patients suffering CNS side effects on lipid soluble beta blockers were changed to atenolol in 92% the CNS side effects either disappeared or were markedly diminished.¹⁰

3 Excretion Hydrophilic beta blockers tend to be poorly metabolized. Thus atenolol is excreted almost totally unchanged by the kidney. Ninety to 95% can be recovered in the urine within 48 hours of intravenous administration.¹ A small amount 5 to 10% is metabolized by the liver to form a hydroxy metabolite and a glucuronide both of which have only weak pharmacological action.¹ In the case of lipophilic beta blockers such as propranolol alprenolol metoprolol and oxprenolol some of the orally administered drug fails to reach the systemic circulation because the drug in the portal vein is taken up and removed by the liver. This is termed the 'first

pass effect'. These drugs are almost wholly metabolized by the liver^{23, 24} forming metabolites which are weakly pharmacologically active.

The plasma half life of a hydrophilic drug like atenolol lengthens with kidney dysfunction,²⁵ with half lives of 50 hours in patients with very severe dysfunction (glomerular filtration rate 0 to 10 ml/minute). However at glomerular filtration rates (GFRs) greater than about 30 ml/minute or a serum creatinine less than 2.5 mg % or 300 μ mol/L there is no significant accumulation of the drug in the blood.^{26, 27} Lipophilic beta blockers when given to patients with renal failure theoretically should not accumulate. However hepatic function and with it the first pass effect appears to be impaired in patients with severe renal failure so that even lipophilic beta blockers like propranolol and metoprolol appear at substantially higher peak blood levels than in patients with normal renal function.^{28, 29} There is also a marked accumulation of metabolites at this time.

Elderly (70 years+) compared to young subjects have a decrease (about 40%) in both renal and hepatic function. As a drug such as atenolol is virtually unmetabolized by the liver and does not accumulate significantly at GFRs greater than about 35 ml/minute the aging effects upon the kidney and liver should be of little consequence. Indeed it has been shown that the pharmacokinetics of a hydrophilic beta blocker (practolol) are similar in both the young and elderly.³⁰ In the elderly liver metabolism of a lipophilic agent such as propranolol is impaired so that blood levels of the parent drug are increased some fourfold with chronic dosing in the elderly.³¹ With metoprolol there is pronounced inter individual variation in peak plasma levels in the elderly.³²

Clinical implications

a RENAL FAILURE Patients with normal or mild renal dysfunction (GFR greater than about 35 ml/minute or a serum creatinine of less than 2.5 mg % or < 300 μ mol/L) do not accumulate (to a significant degree) hydrophilic beta blockers such as atenolol.³³ Thus a normal dosing regimen may be recommended. Patients with moderate (GFR 10 to 35 ml/minute or serum creatinine between 2.5 and 5.0 mg % or 300 to 600 μ mol/L) and severe (GFR < 10 ml/minute or serum creatinine > 5.0 mg % or > 600 μ mol/L) renal dysfunction do accumulate atenolol with blood levels plateauing out in severe cases at about 2 to

Table II Concentration of beta blockers (chronic oral administration) in plasma cerebrospinal fluid (CSF) and brain—in man†

| Beta blocker (BB) (dose) | No | Plasma conc ng/ml | | CSF conc ng/ml | | Brain conc ng/g | | Mean plasma/CSF ratio | Mean brain/plasma ratio | Mean brain/CSF ratio |
|-------------------------------|----|----------------------|---------------|-------------------|----------------|--------------------|---------------|-----------------------------|-------------------------------|----------------------------|
| | | Indiv values | Mean value | Indiv values | Mean value | Indiv values | Mean value | | | |
| Propranolol (80 mg b.i.d.) | 3 | 17 | | 3 | | 830 | | 10 | 17 | 171 |
| | | 7 ^b | 153 | 3 | 15 | 1183 | 2561 | | | |
| | | 3 ^b 0 | | 38 | | 5669 | | | | |
| Metoprolol (100 mg b.i.d.) | 1 | 150 | 150 | 130 | 130 | 2108 | 2108 | 1 | 14 | 16 |
| Atenolol (100 mg o.d.) | 3 | 500 | | 72 | | 100 | | 15 | 0.1 | 2 |
| | | 300 | 1000 | 40 | 6 ^c | 140 | 133 | | | |
| | | 2200 | | 85 | | 160 | | | | |

^a = limit of detection† Reproduced with permission from Cruckshank et al.²³

body compartments^a depends upon both lipophilicity and plasma protein binding. Thus metoprolol being moderately lipophilic and poorly protein bound has a large volume of distribution = 5.6 L/kg, propranolol though having a high lipophilicity is highly protein bound and has a volume of distribution of 3.6 L/kg, atenolol although being lowly protein bound is highly hydrophilic and thus has a very low volume of distribution at 0.7 L/kg.

Of particular note is the very low concentration of hydrophilic atenolol in the central nervous system (CNS) in rat, cat and man.²⁴ This is in contrast to both the lipid soluble propranolol and metoprolol^{2,3} (see Table II and Figs 2A and 2B). It should be noted that the concentration of the beta blockers in the cerebrospinal fluid (CSF) is a poor predictor of brain concentration.

Beta blockers are distributed within the blood/CSF/brain compartments according to the model in Fig 3. Thus in Table II the very low CSF levels of propranolol and metoprolol correspond to the approximate 10% and 90% respectively of free drug in the plasma. The very high brain concentration of both propranolol and metoprolol (about 20 times higher than that of atenolol) reflects the high affinity of the brain for these lipophilic agents. Early results indicate that oxprenolol, another lipophilic beta blocker, also appears at higher concentration in brain tissue. Distribution of the lipophilic beta blockers within the blood/CSF/brain compartments occurs within minutes.²⁵ In contrast, hydrophilic atenolol

crosses the blood brain barrier with difficulty and equilibration occurs more slowly (Fig 4). As the CSF in man is completely changed about every 10 hours, atenolol's concentration may be kept low by means of a continual washout or sink effect.² Indeed the CSF and brain concentrations seem to settle at about one fifth to one tenth of peak blood values (which occur 2 to 4 hours post dosing). Thus unlike the situation with lipophilic beta blockers, with atenolol the brain appears to be buffered against peak plasma levels.

Another point of interest is the distribution of various beta blockers in lung tissue relative to blood.⁵ Table III shows a list of lung/blood concentration ratios with lipid soluble drugs appearing in high and highly water soluble drugs in low concentrations in lung tissue. The authors offer a possible explanation of cardioselectivity with the water soluble agent (in contrast to the lipid soluble agent) never attaining a high concentration in the vicinity of the beta₂ receptor. However, on this basis, sotalol and nadolol would also be selective, which is not the case.

Clinical implications

PREDICTABILITY OF ACTION. A drug which is poorly protein bound will not be affected by either disease states which alter plasma protein concentrations and ratios or by other drugs which may compete for protein binding sites. This should contribute to such a drug's predictability in the clinic.

CNS SIDE EFFECTS. The low concentration of a hydrophilic drug in the brain relative to lipophilic agents possibly explains the low inci-

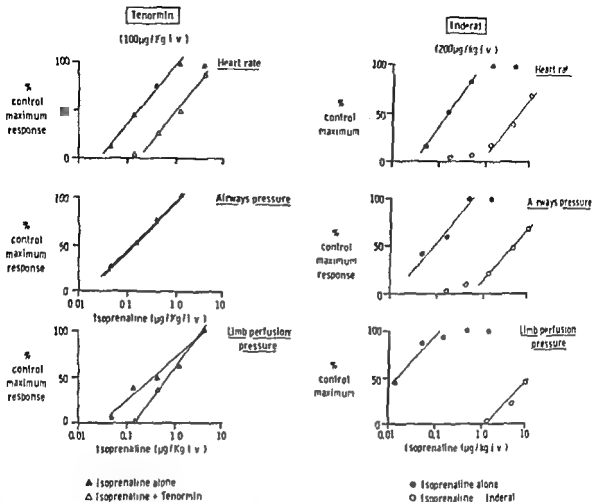


Fig 5 Effect of propranolol and atenolol on heart rate (beta 1), airways pressure (beta 2) and limb perfusion pressure changes resulting from increasing isoprenaline dosage

tions occurring in severe renal failure the cumulative beta blocking effect will be substantial. This is a further possible reason for reducing the dose of lipophilic liver metabolized beta blockers in severe renal failure.

THE ELDERLY Compatible with the fact that the pharmacokinetics of hydrophilic beta blockers are similar in the young and the elderly is the observation that the incidence of side effects was the same in young, middle and old age groups.⁴³ In contrast, lipophilic agents have been reported to produce side effects at a higher incidence in the elderly as compared to the young.⁴

Pharmacodynamics

Beta 1 blockade

1 Cardiovascular

a HEMODYNAMICS All cardiac beta blockers by definition competitively block beta 1 receptors in the heart with the result that there is a slowing of the heart rate and a decrease in

contractility. Beta blockade is best demonstrated at the high heart rates associated with moderate to severe exercise as resting heart rates are influenced by vagal tone. As stroke volume tends to remain unchanged or possibly slightly increased there is a fall in cardiac output of about 20% at maximal beta blockade. The possession of intrinsic sympathomimetic activity (ISA) will tend to be associated with higher heart rates and a lesser fall in cardiac output.⁴⁴ The fall in cardiac output is initially not accompanied by a fall in blood pressure owing to an alpha mediated reflex increase in peripheral resistance.⁴⁵ Later probably after only 2 to 3 hours the peripheral resistance falls and is accompanied by a decrease in blood pressure. Subjects whose blood pressure does not eventually fall still maintain the initial beta blocker induced increase in peripheral resistance. These hemodynamic changes persist for at least one year after starting the beta blocker therapy (atenolol).⁴

CSF/Brain Concentrations of Atenolol and Metoprolol
Anaesthetised cats drugs given i.v. 1 mg/kg

van Zwieten and Timmermans 1979

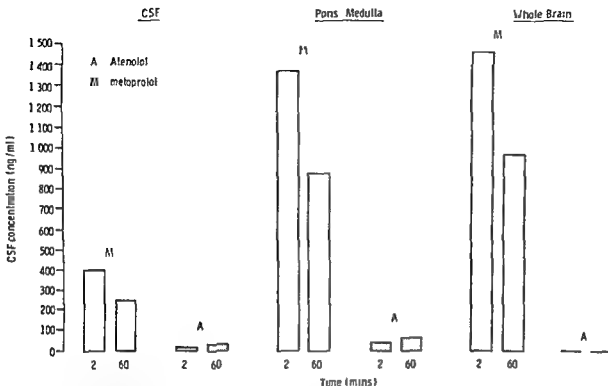


Fig 4 Cerebrospinal fluid/brain concentrations of atenolol and metoprolol. Anesthetized cats, drugs given intravenously 1 mg/kg.

4 weeks³. Although patients with moderate or severe renal failure tolerate the high blood concentration of atenolol perfectly well, blood levels similar to those in the normal therapeutic range are desirable, particularly if the benefits of cardioselectivity (which are dose related) are to be retained. The conclusions of recent studies on hydrophilic atenolol and renal dysfunction indicated that normal blood levels could be obtained in patients with renal failure and that (1) patients with a GFR of greater than 35 ml/minute should have the normal dose (2) patients with a GFR of 10 to 35 ml/minute should have half the normal dose or the whole dose on alternate days (3) patients with a GFR < 10 ml/minute should have half the normal dose on alternate days and (4) patients on hemodialysis 2 to 3 times a week should be given half the normal daily dose after every hemodialysis (under hospital supervision since marked falls in blood pressure can occur).

Because hepatic function appears to be somewhat unimpaired in patients with severe renal dys-

Table IV Mean cardioselectivity indices (pA cardiac β_1 receptor/pA bronchial β_2 receptor) in vivo (dog) and in vitro (animal and human)*

| Beta blocker | Mean cardioselectivity indices | |
|--------------|--------------------------------|----------|
| | In vivo | In vitro |
| Atenolol | 1.64 | 1.71 |
| Practolol | 1.59 | 1.70 |
| Metoprolol | 1.54 | 1.46 |
| Acebutolol | 1.40 | 1.59 |
| Pindolol | 0.58 | 0.30 |
| Propranolol | 0.45 | 0.32 |

* R produced with permission from Hartas, H II

function, lipophilic β blockers (propranolol and metoprolol) should also be given in reduced dosage³⁻⁵ in such cases. With the lipophilic β blockers, there is also a marked increase in plasma concentration of liver metabolites^{3,6}. Although these metabolites have only weak pharmacological activity, it seems likely that at the concentra-

Dose Response Curve of Bronchial Muscle

Benson 1976

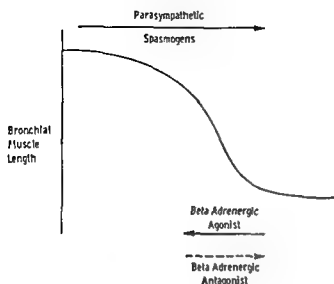


Fig 6 Dose response curve of bronchial muscle

of beta 2 receptors generally has *potentially* detrimental effects. It is in these situations that a cardioselective beta blocker might be considered preferable to a non cardioselective beta blocker.

Beta 2 blockade

I. Bronchus Ideally claims for cardioselectivity should be based on data showing that the beta blocker inhibits the beta 1 effects of an agonist upon the heart while having little or no effect upon peripheral beta 2 effects—e.g. bronchodilation or vasodilatation. Such circumstances pertained in the dog model shown in Fig 5 where propranolol produced both beta 1 and beta 2 blockade by shifting the isoprenaline/heart rate and airways pressure dose response curves to the right while atenolol modified only the beta 1 effects. Metoprolol behaves in a similar fashion to atenolol.⁶ Harms, using *in vitro* and *in vivo* models has presented a table of cardioselective indices (see Table IV). This table is in roughly the reverse order of Hemsworth's table of lung/blood concentration ratios (Table III).

Tattersfield and associates¹ have devised a model in normal volunteers whereby beta 2 specificity or lack of it may be estimated. The volunteers were given increasing doses of an inhaled beta 2 stimulant (salbutamol) and the effect upon airways conductance was measured in a whole body plethysmograph. All subjects were later exposed to various beta blockers at two dose levels. The doses of the various agents were

chosen at levels thought to be approximately equipotent and clinically relevant. Two hours after administration of the beta blocker the subjects were given salbutamol in increasing doses the effect again being measured in the whole body plethysmograph. Dose ratios were estimated the dose ratio being that dose of salbutamol required to produce 50% maximum response (increase in airways conductance) for each drug and dividing this by the dose required to produce 50% response on placebo. Table V shows dose ratios and it can be seen that atenolol and practolol caused the least interference with the salbutamol dose response curves and propranolol the most interference. Cardioselectivity was illustrated in the case of atenolol by the fact that it caused the greatest fall in exercise heart rate (beta 1) but with practolol the least interference with airways conductance (beta 2). It can be seen that the higher the dose of a beta blocker the more of a beta 2 stimulant (salbutamol) is required to overcome the detrimental effects on airways conductance. This confirms that the benefits of cardioselectivity tend to be lost at higher doses.¹

Clinical implications Work by Benson and colleagues^{12, 13} (Fig 6) has shown that bronchi which are not dependent upon sympathetic drive to maintain their caliber will be little affected by potential spasmogens e.g. beta 2 blockade. Thus results of studies carried out on normal subjects whose bronchi are unstimulated must be regarded as potentially misleading. Indeed it is likely that asthmatic subjects who are well with a normal or approaching normal FEV₁ (forced expiratory volume) are able to tolerate beta 2 blockade.¹³ However patients whose bronchi are dependent upon sympathetic tone to maintain their caliber—i.e. who fall on the steep part of Benson's dose response curve—are at definite risk from beta 2 blockade. A study in a group of such patients¹⁴ (Fig 7) demonstrated two important facts. Under circumstances where seven different orally administered beta blockers at clinically relevant doses had produced approximately the same amount of beta 1 blockade (suppression of standing pulse rate and inhibition of the effect of isoprenaline upon the pulse rate) (1) a relatively highly cardioselective beta blocker was least likely to cause important bronchoconstriction and (2) such a beta blocker (in contrast to non-selective agents) almost completely preserved the

Table V Beta blocker dose ratios—modifying effect of beta blockers upon beta β stimulated bronchodilatation (airways conductance)*

| Beta blocker | Placebo | | Practolol | | Atenolol | | Acebutolol | | Labetalol | | Propranolol | |
|----------------------|---------|---|-----------|------|----------|------|------------|-----|-----------|------|-------------|------|
| Dose (mg) | — | — | 100 | 200 | 50 | 100 | 100 | 200 | 150 | 300 | 40 | 80 |
| Dose ratios | 1.00 | — | 1.11 | 2.36 | 1.36 | 1.94 | 2.48 | 3.9 | 2.10 | 4.10 | 23.0 | 55.9 |
| Exercise pulse rates | 158 | — | 127 | 135 | 116 | 104 | 127 | 115 | 135 | 122 | 123 | 116 |

* Produced with permission from Tattersfield A E, Ma L y A D, Gribbin H H and Baldwin C J

BIOLOGICAL HALF LIFE Hydrophilic mainly orally excreted beta blockers tend to have long plasma or chemical half lives. On the other hand lipophilic mainly liver metabolized beta blockers tend to have short plasma half lives. The plasma or chemical half life is independent of dose contrasting with the biological or pharmacological half life which is dose dependent. For example a beta blocker such as atenolol with a long chemical half life (6 to 9 hours) when administered in a relatively low dose of 50 mg will rise to beta blockade 24 hours after the dose such as was about 30% of maximum (decrease in heart rate three hours after the dose). By doubling the dose it was possible to achieve about 70% maximum blockade 24 hours after the dose. The same principle applies to the beta blockers with short chemical half lives. However if biological effect is required over a 24 hour period an agent with a short chemical half life will need to be administered at high dosage relative to an agent with a long chemical half life even though the agents might be equipotent milligram for milligram in producing maximal beta blockade at 2 to 3 hours post dose. For example metoprolol with a short chemical half life and atenolol with a longer chemical half life are considered to be equipotent milligram for milligram in suppressing exercise heart rate or systolic blood pressure 2 to 3 hours after dosing. Whereas atenolol (dose 100 mg) produced a substantial increase in both exercise heart rate and systolic blood pressure 24 hours post dosing little or no effect remained 12 to 24 hours after the same dose of metoprolol.^{3,4} However equipotency of effect after 24 hours could be achieved either by tripling the single dose of metoprolol or by giving the dose once daily.⁵

ELECTROPHYSIOLOGY Both cardioselective atenolol and non selective propranolol have the same effect on the sinus and AV nodes. Both agents equally slow the sinus rate prolong sinoatrial and AV nodal conduction time (A-H in His bundle ECG) and prolong the effective refractory

period of the A-V node.^{6,7} Neither the conduction time within the atrium, the His Bundle and ventricle nor the refractory periods of these compartments are altered by atenolol or propranolol. However one study indicated that atenolol but not propranolol increased atrial refractoriness.⁸

2 Renin Renin release is probably primarily a beta 1 effect thus both cardioselective and non cardioselective beta blockers equally suppress plasma renin activity (PRA).^{9,10} Earlier claims that atenolol had no effect on the renin-angiotensin system¹¹ results from measurements on plasma renin concentration (not PRA) which was not affected by atenolol.

3 Intraocular pressure A decrease in production of aqueous humor arises after beta 1 blockade.¹² Thus both non-selective and cardioselective beta blockers lower intraocular pressure with equal facility.

4 Anxiety/tremor The peripheral signs of both anxiety and thyrotoxicosis¹³ seem to be blocked equally well by both non selective propranolol and cardioselective atenolol.

Clinical implications Clinical states which benefit primarily from blockade of beta 1 receptors such as angina, dysrhythmias, glaucoma, high renin situations and possibly anxiety and thyrotoxicosis will be equally affected by both cardioselective and non cardioselective agents. In hypertension and indeed angina it should be possible to administer a hydrophilic beta blocker on a once daily basis at relatively low dosage. This should hopefully help foster good patient compliance in adhering to the therapy. Moreover the benefits of cardioselectivity will still be maintained at low dosage (see below) which will not be the case if as in the case of a cardioselective lipophilic agent with a short clinical or plasma half life dosage is increased in order to achieve 24 hour effect.

In conditions that possibly benefit from beta 2 blockade (migraine)¹⁴ cardioselective beta blockers may have no useful action. However blockade

Dose Response Curve of Bronchial Muscle

Benson 1976

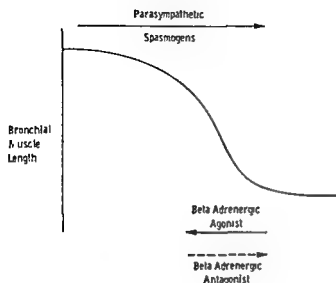


Fig 1 Dose response curve of bronchial muscle

of beta 2 receptors generally has *potentially* detrimental effects. It is in these situations that a cardioselective beta blocker might be considered preferable to a non cardioselective beta blocker.

Beta 2 blockade

I. Bronchus. Ideally, claims for cardioselectivity should be based on data showing that the beta blocker inhibits the beta 1 effects of an agonist upon the heart while having little or no effect upon peripheral beta 2 effects—e.g. bronchodilation or vasodilatation. Such circumstances pertained in the dog model shown in Fig 5 where propranolol produced both beta 1 and beta 2 blockade by shifting the isoprenaline/heart rate and airways pressure dose response curves to the right while atenolol modified only the beta 1 effects. Metoprolol behaves in a similar fashion to atenolol.⁶ Harms⁹ using *in vitro* and *in vivo* models has presented a table of cardioselective indices (see Table IV). This table is in roughly the reverse order of Hemsworth's table of lung/blood concentration ratios (Table III).

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chosen at levels thought to be approximately equipotent and clinically relevant. Two hours after administration of the beta blocker the subjects were given salbutamol in increasing doses the effect again being measured in the whole body plethysmograph. Dose ratios were estimated the dose ratio being that dose of salbutamol required to produce 50% maximum response (increase in airways conductance) for each drug and dividing this by the dose required to produce 50% response on placebo. Table V shows dose ratios and it can be seen that atenolol and practolol caused the least interference with the salbutamol dose response curves and propranolol the most interference. Cardioselectivity was illustrated in the case of atenolol by the fact that it caused the greatest fall in exercise heart rate (beta 1) but with practolol the least interference with airways conductance (beta 2). It can be seen that the higher the dose of a beta blocker the more of a beta 2 stimulant (salbutamol) is required to overcome the detrimental effects on airways conductance. This confirms that the benefits of cardioselectivity tend to be lost at higher doses.⁷

Clinical implications. Work by Benson and colleagues^{12, 14} (Fig 6) has shown that bronchi which are not dependent upon sympathetic drive to maintain their caliber will be little affected by potential spasmogens e.g. beta 2 blockade. Thus, results of studies carried out on normal subjects whose bronchi are unstimulated must be regarded as potentially misleading. Indeed it is likely that asthmatic subjects who are well with a normal or approaching normal FEV₁ (forced expiratory volume) are able to tolerate beta 2 blockade.¹² However patients whose bronchi are dependent upon sympathetic tone to maintain their caliber—i.e. who fall on the steep part of Benson's dose response curve—are at definite risk from beta 2 blockade. A study in a group of such patients⁷ (Fig 7) demonstrated two important facts. Under circumstances where seven different orally administered beta blockers at clinically relevant doses had produced approximately the same amount of beta 1 blockade (suppression of standing pulse rate and inhibition of the effect of isoprenaline upon the pulse rate) (1) a relatively highly cardioselective beta blocker was least likely to cause important bronchoconstriction and (2) such a beta blocker (in contrast to non-selective agents) almost completely preserved the

Effect of Beta Blocker and Isoprenaline upon FEV₁ in 10 Responding (Labile) Asthmatic Patients

Wythenshawe and Southampton 1976

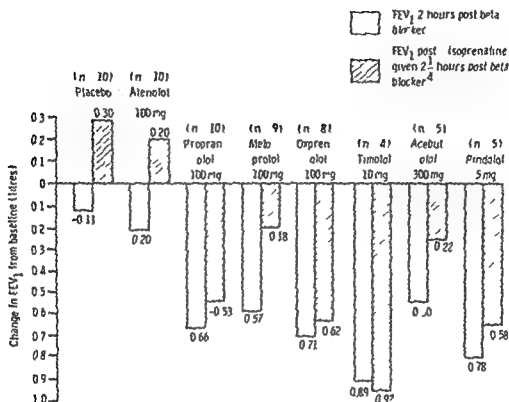


Fig 7 Effect of beta blocker and isoprenaline upon forced expiratory volume (FEV₁) in 10 responding (labile) asthmatic patients

2 bronchodilator action of isoprenaline should be emphasized that an asthmatic patient who is well and who falls on the flat part of Benson's dose response curve might be from beta 2 blockade at a different point in the curve. This fact is well illustrated (Benson personal communication) by the asthmatic patient who had his FEV₁ was 4.2 liters tolerated propranolol 100 mg well with no change in FEV₁. However 4 months later (on no therapy) when he was given with an FEV₁ of 2.9 liters he was unable to tolerate propranolol 80 mg. propranolol reduced his FEV₁ to fall to 1.7 liters and precipitated severe asthma. It is thus recommended that non-selective beta blocker should never be given to a patient with reversible airways obstruction.

Cardioselective beta blockers like atenolol, metoprolol do not confer absolute safety. There will be occasional asthmatic patients who respond in an adverse way and it is recom-

mended that atenolol and metoprolol should be prescribed alongside a beta 2 stimulant such as isoprenaline, salbutamol or terbutaline in symptomatic asthmatic patients. Another point worth emphasizing again is that cardioselectivity is a dose dependent property. Thus the dose of a cardioselective agent should be kept as low as possible in patients at risk, otherwise the advantages of cardioselectivity will be diminished."

Finally, one ought to be aware of the possible role of metabolites in determining the cardioselective profile of a beta blocker. Thus the acetyl metabolite of acebutolol which appears in the plasma at higher concentrations than its parent drug is probably less cardioselective than acebutolol itself."

II Peripheral blood vessels: Fig 5 showed that the non-selective beta blocker not only competitively inhibited the beta 2 associated increase in bronchial airflow but also competitively inhibited the beta 2 associated increase in peripheral

unction during treatment with a non selective compared to a cardioselective beta blocking drug this may be of importance in patients with renal disease

It would thus seem reasonable to prescribe a cardioselective agent to patients with renal dysfunction who require beta blocker therapy. However a non selective beta blocker (nadolol)¹¹¹ has been claimed to actually increase renal blood flow. Such a claim is surprising and needs confirmation.

6 MIGRAINE Non selective propranolol is almost certainly effective in treating migraine.¹¹² Evidence to date (Behan personal communication) suggests that a cardioselective beta blocker is probably not effective in treating migraine. However well controlled studies are required before this suspicion becomes fact.

III Metabolic

a INSULIN SECRETION Resting insulin levels seem to be unaffected by beta blockers.¹¹³ However stimulated insulin secretion¹¹⁴ is markedly suppressed by non selective beta blockers such as propranolol and only slightly suppressed by atenolol.

b GLYCOGENOLYSIS AND GLUCONEOGENESIS It has been shown¹¹⁵ that the return of blood sugar to normal after insulin induced hypoglycemia was delayed by non selective but not by cardioselective beta blockade. There are two possible explanations of this: (1) that a beta 2 aspect of glycogenolysis is blocked by the non selective and not by the cardioselective beta blocker thus impairing the liver's ability to replenish the blood sugar and (2) non selective but not cardioselective beta blockers block lactic acid and glycerol (inhibits lipolysis) release from muscle¹¹⁶ and thus the liver is denied substrate for gluconeogenesis.

c. FREE FATTY ACIDS (FFAs) Basal FFA blood levels are suppressed equally by both selective and non selective beta blockers¹¹⁷ although this effect appears to diminish in time. However a stress induced increase in FFAs tends to be better suppressed by a non selective beta blocker¹¹⁸ suggesting a definite beta 2 component.

Clinical implications

a. DIABETES The effect of basal insulin secretion is unaffected by beta blockers. Stimulated insulin secretion is markedly suppressed by non selective beta blockers. This latter occurrence

might explain the observations of Waal Maning¹¹⁹ in which some patients while on propranolol had chemical diabetes but on metoprolol they had a normal glucose tolerance test. These observations have not been confirmed in another study¹²⁰ in which in fact the post propranolol blood sugar tended to be somewhat lower than after a cardioselective drug (atenolol).

The importance of hypoglycemia associated with propranolol therapy has probably been much exaggerated¹²¹ and most diabetic patients may be given this drug with safety.¹²² However hypoglycemia is undoubtedly a rare but important side effect with non selective beta blockade¹²³ particularly for diabetic patients on insulin¹²⁴ fasting subjects (particularly children)¹²⁵ post myocardial infarction patients¹²⁶ and possibly in patients undergoing hemodialysis.¹²⁷ Moreover the speed of recovery of the blood sugar to normal is impeded by non selective beta blockers in contrast to cardioselective agents.¹²⁸ Interestingly hypoglycemic symptoms such as sweating and pallor appear to be unaffected by beta blockers. The tachycardia is however suppressed more so by non selective than by cardioselective agents. These observations have led these authors and others¹²⁹ to conclude that for the insulin-dependent diabetic patient requiring a beta blocker a cardioselective agent would be preferable.

b. FREE FATTY ACIDS It has been suggested by some that increased FFA levels in the post infarction period might be causing important dysrhythmias.¹³⁰ However in a randomized study involving oral administration of either atenolol, propranolol or placebo¹³¹ within hours of myocardial infarction (and continuing for one year) 24 hour ECG taping showed that the number of important ventricular dysrhythmias was the same for both agents (and indeed differed but little from placebo). It would thus appear likely that a non selective beta blocker will not confer an advantage in this area in terms of post infarction dysrhythmia prevention or indeed in dysrhythmias not associated with myocardial infarction.¹³²

Suggestions that high plasma FFA levels will increase atheroma formation and that a non selective beta blocker (in contrast to a selective agent) will hinder this process are entirely speculative.

dilation might theoretically be expected to produce a lower blood pressure than a beta blocker that does not.

Resting blood pressure (supine and stand

most studies^{2,100} in which orally administered atenolol has been compared with non selective β blockers on a cross-over basis have indicated that atenolol is a superior antihypertensive agent in all of these studies. Atenolol was given in the daily doses and the non selective agent was given either once^{97,101} twice⁹⁸ or four times⁹⁹ daily.

In the remaining three studies^{97,101} both atenolol and the non selective agents were given on a twice daily basis. Metoprolol also claims a similar advantage.¹⁰² However other studies employing a crossover design and twice daily dosing have indicated that little difference exists¹⁰³ between the antihypertensive effect of selective and non selective agents. On balance it is likely that a cardioselective beta blocker is slightly more effective in lowering diastolic blood pressure.

Exercise blood pressure

Dynamic. It has been indicated that cardioselective beta blockers administered on a crossover basis are either intravenously⁹⁷ or orally¹⁰⁴ superior to non selective agents in lowering the blood pressure associated with dynamic exercise.^{97,10,104} However more well conducted studies are required before these claims of atenolol and metoprolol can be regarded as proven. Isometric. Claims have also been made that orally administered cardioselective beta blockers are more effective in preventing the rise in blood pressure associated with handgrip exercise.⁹⁷ However others have not confirmed this¹⁰⁵ and the question must remain unanswered at present.

Stress hypertension

Mental. Claims have been made⁹⁷ that orally administered cardioselective agents are more effective than non selective agents in preventing the rise in blood pressure associated with mental stress. But confirmation of these results has not yet forthcoming¹⁰⁷ and the question must remain open. One study⁹⁸ has shown that non selective blockade (intravenous propranolol) used to abolish a diastolic pressor effect during mental stress.

Insulin treated diabetic. During insulin hypoglycemia cardiovascular changes occur which are similar to those occurring after adrenaline infusion.

Insulin¹⁰⁸. Intravenous administration of a non selective beta blocker under these conditions blocks not only beta 1 receptors but also beta 2 vasodilator receptors with the result that a diastolic pressor response of some 10 to 15 mm Hg occurs.¹⁰⁹ In contrast the pressor response is absent or diminished with a cardioselective beta blocker (metoprolol) administered either intravenously¹¹⁰ or orally.¹¹¹ Thus for insulin treated diabetic patients requiring a beta blocker — the choice of a cardioselective agent is possibly preferable.

Smoking. The act of smoking as with insulin induced hypoglycemia is associated with increased adrenaline secretion, tachycardia and an increase in both systolic and diastolic blood pressure (Fig 8). Intravenous administration of a non selective beta blocker during smoking did not diminish the systolic rise in blood pressure and caused a marked diastolic pressor response (15 to 20 mm Hg). In contrast cardioselective atenolol lowered the systolic blood pressure and did not cause a diastolic pressor response. If these observations are confirmed in chronic oral studies there could be important implications in the choice of agent for the patient who insists on smoking and who also requires beta blocker therapy.

4. ANGINA. Parratt and Marshall's work in animals has suggested that beta blockers with ISA and/or cardioselectivity in contrast to non selective beta blockers, are less likely to embarrass coronary hemodynamics. Such a property might theoretically be beneficial to the anginal patient. Astrom and Vallin¹¹² have in fact claimed such an advantage for atenolol (5 mg intravenously) over propranolol (5 mg intravenously) but explain this on the basis that atenolol was associated with a lesser rise in exercise blood pressure and thus lessened the afterload on the heart. However other studies that have compared oral atenolol with propranolol and oxprenolol¹¹³ on a randomized crossover basis have shown no difference in antianginal effect.

5. RENAL FUNCTION. The minimal effect of cardioselective relative to non selective beta blockers upon effective renal plasma flow and creatinine clearance¹¹⁴ has led one group to conclude that treatment with atenolol would appear not to cause significant reduction of renal function and another investigator¹¹⁵ to declare that he found a greater deterioration in renal

selective in contrast to a non selective beta blocker (with no ISA) Some patients with intermittent claudication thus will have a greater exercise tolerance with a cardioselective beta blocker

4 *Antihypertensive control* Because cardioselective beta blockers preserve beta 2 vasodilator action they are possibly slightly more effective antihypertensive agents than are non selective beta blockers

5 *Stress hypertension* Hypertension associated with increased adrenaline secretion—e.g. insulin induced hypoglycemia smoking and possibly mental stress is exacerbated (diastolic pressure effect) by a non selective beta blocker This is not the case with a cardioselective beta blocker

6 *Renal function* Renal function (effective renal plasma flow and creatinine clearance) is less compromised on cardioselective compared to non selective beta blockers (? nadolol excepted) This fact might be of importance to patients with already impaired renal function

7 *Migraine* Non selective propranolol is an effective prophylactic drug for migraine It is doubtful if cardioselective beta blockers will be effective

8 *Blood sugar* The majority of diabetic patients tolerate propranolol well The return of blood sugar to normal after insulin induced hypoglycemia is dependent to some extent on beta 2 receptor integrity (glycogenolysis and gluconeogenesis) A non selective beta blocker in contrast to a cardioselective beta blocker prolongs the hypoglycemic period Thus for patients at risk from hypoglycemia who require beta blocker therapy a cardioselective agent is probably preferable

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Uterus Animal studies suggest that beta 2 increases the frequency and strength of of the gravid uterus¹³¹

AL IMPLICATIONS Most studies^{132, 13} ate that beta blockers (propranolol and prenolol) may be given to the pregnant female + harm to mother of child Indeed one idy¹³³ indicated a superiority of the beta block (oxprenolol) over methyldopa the former ig associated with heavier placentas and birth

Some^{133, 14} suggest that beta blockers ght harm the foetus However the fears that a n selective beta blocker might precipitate pre ture contractions and miscarriage have not borne out

Cardioselective beta blockers tend as a group be hydrophilic However hydrophilicity is not essential factor for the expression of cardiose

I kewise non selective beta blockers are lly lipophilic but lipophilicity is not an factor for expression of non selectivity gh beta blockers as a group are effective and use few troublesome side effects an agent is cardioselective hydrophilic and non olized has in contrast to one which is n selective lipid soluble and metabolized sev advantages in certain clinical areas

inetic (hydrophilicity versus lipo
philicity)

1 Blood levels and length of action Consistent tween patient peak blood levels (only v to fourfold variation compared to twenty d with liver metabolized agents like proprano and metoprolol) render a hydrophilic beta such as atenolol a very predictable drug the clinical situation and are probably contrib ing to its narrow dose range Being unmetabo l and renal excreted hydrophilic beta block have a long biological action which enables a dose to be given on a once daily basis + in 24 hour cover for both hypertension angina

The brain In man very little atenolol (hy) enters the brain (about one twentieth the concentration of a lipophilic beta blocker) has a brain/blood ratio of approximately 0.1 l d to 17.1 and 14.1 with propranolol and prolol (both lipophilic) respectively This ssibly accounts for (1) the low incidence of side

effects relating to the CNS and (2) the disappear ance of CNS side effects on changing from lipo philic beta blockers to atenolol

3 The kidney Hydrophilic beta blockers such as atenolol and nadolol are excreted virtually unmetabolized by the kidney However in the case of atenolol at glomerular filtration rates above 35 ml/minute (or serum creatinine of < 2.5 mg % or 300 mmol/L) there is no signifi cant drug accumulation and the normal dose may be given Significant accumulation occurs in mod erate to severe renal failure so that in order to achieve optimal therapeutic blood levels at glo merular filtration rates between 10 and 35 ml / minute (serum creatinine 2.5 to 5.0 mg % or 300 to 600 mmol/L) the daily dose should be halved and at glomerular filtration rates less than 10 ml/minute (serum creatinine > 5.0 mg % or 600 mmol/L) half the daily dose should be given on alternate days With lipophilic liver metabolized beta blockers like propranolol and metoprolol there is likewise a tendency for increased blood levels in severe renal failure (due to the accom panying liver dysfunction) These higher blood levels plus a marked accumulation of metabolites are an indication for dosage reduction

4 The elderly The elderly handle and tolerate hydrophilic beta blockers in a similar fashion to younger subjects Due to the liver dysfunction associated with aging (hepatic blood flow decreased 40 to 50% in the 70 years old subjects) lipophilic beta blockers like propranolol achieve blood levels in the elderly up to fourfold higher than in younger subjects this may account for the possible higher incidence of side effects in the elderly

Pharmacodynamic (cardioselectivity versus non selectivity)

1 Asthma At low doses atenolol and meto prolol are highly cardioselective (cardioselectivity is dose related) and are the beta blockers proba bly least likely to cause a fall in forced expiratory volume (FEV₁) in patients with reversible airways obstruction Also unlike non selective beta blockers they preserve the bronchodilator action of a beta 2 stimulant such as isoprenaline

2 Cold extremities Cold extremities can occur with all beta blockers but the temperature change is minimal on a cardioselective agent

3 Peripheral blood flow Peripheral blood flow during exercise is less compromised with a cardio

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Table I Distribution of patients and control groups

| | No of subjects M/F | Age (years) range mean \pm S D | No of subjects with idiopathic GIT bleeding (%) mean age \pm S D | No of subjects with aortic stenosis (%) mean age \pm S D |
|--|-----------------------|--|---|--|
| Subjects with AS (Case group A) | 1/2 103/49 | 7-74 44.4 \pm 16.3 | 4 (2.6%) 57.5 \pm 6.9 | — |
| Subjects with MS (Control group A) | 1/2 22/97 | 12-77 46.7 \pm 13.1 | 0 | — |
| Subjects with GIT bleeding (Case group B) | 1/4 96/108 | 11-87 57.4 \pm 15.2 | — | 9 (5.8%) 59.9 \pm 7.3 |
| Routinely admitted patients without GIT bleeding (Control group B) | 1/4 73/81 | 17-79 58.4 \pm 14.3 | — | 3 (1.5%) 57.3 \pm 27.5 |

M = male F = female GIT = gastrointestinal tract AS = aortic stenosis MS = mitral stenosis.

Table II Sources of bleeding and incidence of AS in patients with GIT bleeding (Case group B)

| Source of bleeding | No of patients | Subjects with aortic stenosis |
|-------------------------|----------------|-------------------------------|
| Duodenal ulcer | 91 | 1 |
| Diaphragmatic hernia | 15 | 1 |
| Diverticulosis of colon | 5 | 0 |
| GIT tumors | 7 | 0 |
| Esophageal varices | 2 | 0 |
| Drug induced | 7 | 0 |
| Idiopathic | 24 | 7 |

Table III The age distribution according to sex in Case group A (aortic stenosis) and Case Group II (GIT bleeding)

| Age (year) | Case Group A F/M | Case Group B F/M |
|------------|---------------------|---------------------|
| < 20 | 8/13 | 0/2 |
| 21-30 | 5/6 | 2/8 |
| 31-40 | 3/14 | 4/7 |
| 41-50 | 14/22 | 6/17 |
| 51-60 | 10/29 | 18/17 |
| 61-70 | 8/19 | 16/24 |
| 71 | 1/0 | 12/21 |
| Totals | 43/103 | 58/96 |

findings of AS were confirmed by findings at cardiac catheterization. In Case group A, AS was proven at autopsy. In the anemic patient, the systolic murmur was regarded as significant only when it remained following blood transfusion and subsequent restoration of the hemoglobin level to normal values.

Statistical analysis was done using the chi square test.

Results

The distribution of the patients in the four groups is given in Table I and the sources of GIT bleeding in Case group B is given in Table II. In Table III the age and sex distribution of the patients in Case groups A and B are summarized. Seven patients (five males and two females) in Case group A (4.6%) had duodenal ulcer (three of them with melena) and four males (2.6%) had idiopathic GIT bleeding (in three of them repeated laparotomies did not disclose the source of bleeding). Their mean ages were significantly higher than that of the total group A ($p < 0.05$) (Table I). Only four patients (two males two females) of the control group A (2.6%) had duodenal ulcer and none had idiopathic GIT bleeding (Table I). No statistically significant difference was found between the patients with idiopathic GIT bleeding those with duodenal ulcer and the non bleeders regarding the cardiac output valve area, use of anticoagulants or antiplatelet aggregating agents and incidence of diabetes mellitus and arterial hypertension. Syphilis was not detected among the presently examined patients.

Nine patients of Case group B (5.8%) had AS (in five of them the diagnosis was confirmed by autopsy in two by catheterization and in the other two it was based on clinical criteria [a to d]). Their mean age was significantly higher than that of the total Case group B ($p < 0.005$) (Table

stenosis associated with gastrointestinal A survey of 612 patients

udri Shoenfeld M D
hael Eldor M D
Bedarovsky M D
J Levi M D
Pinkhas M D
Tikva Israel

pite the sophisticated procedures used in the
nosis of bleeding from the gastrointestinal
(GIT) it is sometimes impossible to estab-
the source of the bleeding.¹ An association
between GIT bleeding of undetermined source
aortic stenosis (AS) has been reported and
hereby tried to assay the incidence of GIT
bleeding of established and of undetermined origin
among patients with documented AS as well
the incidence of AS in patients with GIT
bleeding of undetermined origin

and methods

he patient material (data as to age and sex are
in Table I) consisted of

Case group A—152 patients with proven AS
underwent cardiac surgery between the years
1971-1978

Control group B—152 patients with proven
aortic stenosis (MS) who underwent cardiac sur-
gery between the years 1971-1975

All patients underwent preoperative cardiac
evaluation in which cardiac output and aortic
mitral valve areas were determined. All the
patients were examined, diagnosed and operated
in the same department. In all of them the
diagnosis was severe enough to warrant opera-
tion. In AS a gradient of at least 60 mm Hg
between the aortic and the ventricular systolic

pressures and in MS all patients were in function-
al Class of late II or III or suffered from arterial
embolizations. In 77 out of the 152 patients with
AS an associated aortic insufficiency was found
while in only 51 out of the 152 patients with MS
was mitral insufficiency also found.

GIT bleeding was defined as a drop of the
hemoglobin to less than 11.5 g/dl in males and
less than 10.5 g/dl in females associated with
either three consequent positive guaiac stool
examinations for the presence of occult blood or
when melena occurred.

All patients with GIT bleeding underwent a
complete GIT x-ray series including routine rec-
toscopies. In 85% of the patients these examina-
tions were performed at least twice. The bleeding
was considered idiopathic when its source was not
detected by the above mentioned examination.
Eight patients had gastroscopies (and in two of
them—colonoscopies) celiac angiography as well
as explorative laparotomy; however even these
procedures failed to establish the source of bleed-
ing. In order to examine the incidence of AS
among patients with idiopathic GIT bleeding two
additional groups of patients were selected:

1. Case group B—154 patients hospitalized for
GIT bleeding between the years 1971 and 1975.

2. Control group B—154 age matched patients
selected from 154 consecutive admissions during
1974 who had no GIT bleeding (Table I).

The diagnosis of AS was established when at
least four of the following criteria were present:
namely (1) systolic aortic ejection murmur radi-
ating to both carotid arteries (2) a low and slow
radial pulse (3) a calcification of the aortic valve
on chest x-rays (4) typical echocardiographic

th D p r t m e t s of I t e r n l M e d i c i n e D i v i s i o n of T h e I s r a e l
h o s p i t a l S u r g e r y t h e S a k l e S h i f f M e d i c a l A v e
B u i l d i n g M e d i c a l C e n t r P e t h T i k I s r a e l
e d f o r p u b l i c a t i o n D e c 5 1 9 7 9
p r i n t e d f o r p u b l i c a t i o n M a y 1 1 1 9 8 0
i t r e q u e s t Y S h o e n f e l d M D D i v i s i o n of I t e r n a l M e d i c i n e
D B i l s o n M e d i c a l C e n t r P e t h T i k I s r a e l

the AS does not justify this major operation Cattell (quoted in Ref 7) proposed a completely different approach namely a blind resection of the ascending colon This mode of treatment seems to be justified by the reports of GIT bleeding in patients with AS found to originate from the right colon *

Summary

A retrospective study was done in order to examine the association between aortic stenosis (AS) and gastrointestinal tract (GIT) bleeding Four groups of patients included a group of 152 patients with AS a control group of 152 patients with MS, and another two groups of 154 patients each with and without GIT bleeding

GIT bleeding of known and of idiopathic sources was significantly more prevalent among patients with AS (three and four patients respectively) than among those with MS (none) More over AS was significantly more prevalent in association with idiopathic GIT bleeding (seven out of 24 29.1%) in comparison to its association with bleeding from a known source (two out of 130 1.5%) and its incidence in routinely admitted patients without GIT bleeding (three out of 154 1.9%)

This study supports the assumption that GIT bleeding may be associated with AS

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IV The age sex and type of valvular defect in 4 groups of patients with aortic stenosis and aortic GI bleeding (AS + IGIB) IGIB + AS AS + duodenal ulcer (DU) and mitral stenosis + DU

| Case No | AS + IGIB (4/152) | | IGIB + AS (7/154) | | AS + DU (7/152) | | | MS + DU (4/152) | | |
|---------|-------------------|-----|-------------------|-----|-----------------|-----|---|-----------------|-----|---|
| | Age | Sex | Age | Sex | Age | Sex | T | Age | Sex | T |
| 1 | 61 | M | 76 | M | 51 | M | C | 71 | M | R |
| 2 | 49 | M | 70 | M | 54 | M | C | 50 | F | R |
| 3 | 61 | M | 63 | M | 20 | M | R | 60 | F | R |
| 4 | 57 | M | 72 | F | 66 | M | C | 69 | M | U |
| 5 | | | 60 | F | 67 | M | C | | | |
| 6 | | | 66 | F | 60 | F | C | | | |
| 7 | | | 82 | F | 41 | F | R | | | |

type of valvular defect R = rheumatic C = calcified U = unclassified

en of them had AS—i.e. 29.1% of the patients with idiopathic GIT bleeding (seven out of 24) in contrast to only 1.5% (two out of 130) in the control group. AS confirmed by autopsy among the patients with an established source of GIT bleed ($p < 0.001$) (Table II). Only three cases of AS were diagnosed (1.9%) were found in the control group B ($p < 0.05$).

The age sex and type of valvular defect in four groups of patients with GIT bleeding and valvular defect are summarized in Table IV.

on

Our presently reported data reaffirm the association between AS and idiopathic GIT bleeding, the latter being significantly more prevalent among patients with AS compared to the control group with MS. In addition, the incidence of AS among our patients with GIT bleeding (Case p B) was significantly higher than among the control group B (nine versus three, Table I). Over almost one third of the idiopathic GIT bleeders had associated AS (Table II), an incidence comparable with the one reported by Williams and Boston.¹

In the present report the mean age of the patients having AS associated with GIT bleeding was significantly higher than that observed in the respective groups (Table I). Assuming that the atherosclerotic process progresses with increasing years, it might be possible that involvement of both the aortic valve and the GIT vessels in atherosclerotic lesions in older patients could be responsible for this peculiar association. Another possible explanation for the GIT bleed

ing might be an ischemic damage to the intestinal vessel walls due to a decreased cardiac output in patients with AS.¹ This possibility could not be supported by our data, i.e. there was a lack of significant differences in cardiac output between GIT bleeders with AS or with MS. The high incidence of syphilis found by Williams and Boston¹ among their patients with AS and idiopathic GIT bleeding was not noted among the presently examined patients. Duodenal ulcer was found in 4.6% of our patients with AS (seven out of 152), a rate significantly higher than in the control group with MS (2.6%). McNamara and Austen⁷ diagnosed duodenal ulcer in 18 of their 26 patients with AS. We are unable to forward a reasonable explanation for this interesting association. Many patients with AS are treated postoperatively with anticoagulants or antiplatelet aggregation agents. Since duodenal ulcers have a propensity to bleed especially when the patient is on anticoagulants, a search for duodenal ulcer might be recommended in every patient with AS facing operation.

In a considerable percentage of patients with AS and GIT bleeding, the GIT x-rays series, endoscopy, angiography, and explorative laparotomy failed to reveal the source of the bleeding.^{5, 7, 9, 10} Some of these quite aggressive diagnostic procedures bear considerable morbidity and mortality and may be dangerous especially in patients with valvular diseases. McNamara and Austen⁷ reported that recurrent episodes of GIT bleeding ceased following aortic valve replacement. However, these patients are frequently afflicted also by other valvular defects, are of an advanced age, and in many of them the severity of

Table 1 Effects of a moderate acute intravenous sodium load on the excretion of various ions in healthy subjects and in hypertensive patients

| | $C \times 100/\text{GFR}$ (%) | | $C \times 100/\text{GFR}$ (%) | | $C_r \times 100/\text{GFR}$ (%) | | $C_{Na} \times 100/\text{GFR}$ (%) | | $C_{K} \times 100/\text{GFR}$ (%) | | $C \times 100/\text{GFR}$ (%) | |
|---------------------|----------------------------------|-------------|----------------------------------|---------------|------------------------------------|-------------|---------------------------------------|-------------|--------------------------------------|--------------|----------------------------------|--------------|
| | N | H | N | H | N | H | N | H | N | H | N | H |
| Baseline | 175 ± 0.68 | 160 ± 0.36 | 1585 ± 3.50 | 1924 ± 1.90* | 420 ± 0.64 | 353 ± 0.52 | 510 ± 0.54 | 414 ± 0.86 | 1072 ± 1.49 | 854 ± 1.48 | 2.73 ± 0.80 | 2.30 ± 0.41 |
| During NaCl loading | 456 ± 2.20 | 564 ± 1.08 | 1409 ± 1.73 | 2319 ± 2.26 | 641 ± 1.87 | 698 ± 1.19 | 726 ± 2.04 | 698 ± 1.36 | 2170 ± 3.21 | 1810 ± 2.18 | 5.68 ± 1.44 | 8.26 ± 1.59 |
| After loading | 478 ± 0.79 | 565 ± 0.73 | 2379 ± 1.64 | 3448 ± 2.57 | 495 ± 0.91 | 485 ± 0.85 | 451 ± 0.47 | 397 ± 0.70 | 3103 ± 3.18 | 2907 ± 2.99 | 6.38 ± 1.13 | 9.06 ± 1.13 |
| Maximal change | 6.29 ± 2.12 | 7.61 ± 1.36 | 14.10 ± 3.97 | 20.76 ± 3.03* | 4.04 ± 1.91 | 6.67 ± 1.33 | 3.64 ± 2.40 | 5.76 ± 1.39 | 23.65 ± 4.00 | 29.08 ± 3.48 | 5.57 ± 0.90 | 14.01 ± 2.67 |
| p < | 0.05 | 0.001 | 0.05 | 0.001 | NS | 0.005 | NS | 0.01 | 0.01 | 0.001 | 0.05 | 0.01 |

N = healthy subjects (n = 4) H = hypertensive patients (n = 9) * = not significant = p < 0.05 (hypertensive vs normal)

Moderate NaCl load = intravenous infusion of 29% NaCl during 60 minutes During NaCl loading = mean of periods II to 6.

After loading = mean of periods 7 to 10 Maximal change = mean of individual maximum (in a single period from 3 III) minus baseline

Data are presented as mean ± SEM

patients with abnormal (low or high) plasma renin activity values¹⁷ were excluded from the study. A part of the study (Protocol I) was carried out in the University Hospital Utrecht The Netherlands and the other part (Protocols II and III) in the János Hospital Budapest Hungary. The investigations were carried out according to the Declaration of Helsinki. The nature of the investigation was fully explained to each person and written consent was obtained from them. All antihypertensive treatments were discontinued 1 month before the study. All participants (except three hypertensive patients) were placed on a diet containing 200 mEq Na per day for 4 to 7 days before the study. In three members of the hypertensive group H (see below) the daily Na intake was 150 mEq.

Protocols

Protocol I Moderate NaCl loading in four healthy subjects (group N₁) and in nine hypertensive patients (group H). Two days before the study 40 µg DDAVP (Mimurn Ferring AB Malmö Sweden) was given intranasally (20 µg into each nostril) three times a day. On the day of the study of 7 A.M. and 11 A.M. 40-40 µg DDAVP were given intranasally. The study began after an overnight fast and water deprivation at 9 A.M. After two 30 minute control clearance periods (baseline study) 1 liter 2.92% NaCl solution (500 mEq Na) was infused during 60 minutes. During this period and in the next hour altogether

six 20 minute clearance periods were run. The study was concluded by two 30 minute periods. Altogether 10 periods were done during 4 hours.

Protocol II/a High NaCl loading by rapid infusion in four healthy subjects (group N₂). The procedure was the same as in Protocol I except 2 liters 2.92% NaCl (1000 mEq Na) were infused during 60 minutes. An intravenous dose of 4 µg DDAVP was given at 9 A.M. in addition to the two intranasal doses given at 7 A.M. and 11 A.M.

Protocol II/b High NaCl loading by rapid infusion in three hypertensive patients (group H₂). The procedure was the same as in Protocol I except 1½ liters 2.92% NaCl were infused during 80 minutes.

Protocol III High NaCl loading by slow infusion in seven healthy subjects (group N₃). Preparatory DDAVP treatment was not given but during the whole experiment 500 mU lysine-vasopressin per hour were infused intravenously. No baseline periods were run. One liter 2.5% NaCl was infused intravenously during the first two hours and 500 ml 5% NaCl was infused during the second two hours. Altogether 854 mEq Na were given. During the last hour one 60 minute clearance period was performed.

Urine was collected by an indwelling catheter. Blood samples were taken through an indwelling venous catheter (Butterfly Abbott) in periods 1, 2, 5, 7 and 9 of Protocols I II/a and II/b and at midpoint of the clearance period of Protocol III.

Renal response to graded intravenous hypertonic NaCl infusion in healthy and hypertensive subjects: dose-related impairment of distal NaCl reabsorption*

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Enhanced sodium excretion after a salt load has been described as exaggerated natriuresis (EN) in patients with various forms of hypertension¹. Its mechanisms and the renal site of impaired sodium reabsorption have been extensively investigated but are increasingly controversial in the recent literature. A primary tubular defect or an abnormal response to volume expansion were considered as possibly responsible for the phenomenon²⁻¹¹ and a predominant role was claimed for both the proximal tubules³⁻⁸ and the distal nephron⁹⁻¹¹. The abnormal renal handling of sodium previously was thought to be characteristic for all patients with essential hypertension but very recently it was postulated as a feature of renin suppression¹²⁻¹⁴. Our preliminary studies suggested that depression of free water reabsorption (T_{H_2O}) was a more sensitive indicator of the altered renal response to acute NaCl loading than EN itself becoming more pronounced with increasing salt load. Furthermore a similar tendency was found also in the healthy persons when very high NaCl loads were used. Therefore the present work was designed to compare the renal responses of healthy subjects and normal renin essential

hypertensive patients to graded acute intravenous hypertonic NaCl loading with special reference to changes in the normal relationship between solute excretion (osmolar clearance C_{osm}) and T_{H_2O} . From such a comparison we expected to exclude an intrinsic tubular abnormality and to demonstrate that EN is an acute renal response abnormally reset to a lower level in the hypertensive patients.

Materials and methods

Participants Studies were performed on 12 patients with uncomplicated essential hypertension (average age 34.3 ± 2.9 (SEM) years) and on 15 healthy volunteers (average age 23.5 ± 1.9 years). In the Protocol I and II studies (see below) six male and two female healthy subjects and 10 male and two female hypertensive patients participated. Protocol III was performed on four male and three female healthy persons. In the hypertensive groups the elevation of blood pressure was from mild to moderate and all patients were free from any demonstrable cardiovascular renal or endocrinological consequences of long standing hypertension. Normal renal function was assessed by urine analysis creatinine clearance and DDAVP¹ concentration test¹⁵. Renal vascular hypertension was ruled out by normal radiorenogram intravenous pyelogram and in certain cases by renal arteriogram. Other forms of secondary hypertension were excluded by appropriate tests including renal biopsy. Hypertensive

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1 Desamino-D-Arginine Vasopressin.

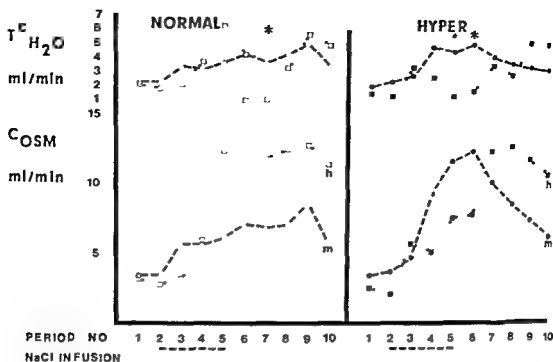


Fig 2 Time course of changes in solute excretion (C_{osm}) and free water reabsorption (T_{H_2O}) during and after acute intravenous NaCl loading in normal subjects and in hypertensive patients. Note the transitory decrease in T_{H_2O} after a high NaCl load (h) apparently not related to changes in C_{osm} in both groups. Moderate NaCl load (m) induced expected changes

Table II Effects of graded acute intravenous sodium loading on the excretion of various ions in healthy subjects

| | $C \times 100/GFR$ (%) | | $C_{Na} \times 100/GFR$ (%) | | $C \times 100/GFR$ (%) | | $C_{Na} \times 100/GFR$ (%) | | $C_i \times 100/GFR$ (%) | | $C_{K} \times 100/GFR$ (%) | |
|---------------------|---------------------------|--------------|--------------------------------|--------------|---------------------------|--------------|--------------------------------|--------------|-----------------------------|--------------|-------------------------------|---------------|
| | N | N | N | N | N | N | N | N | N | N | N | N |
| Baseline | 1.75 ± 0.68 | 1.03 ± 0.18 | 15.85 ± 3.50 | 19.05 ± 4.21 | 4.20 ± 0.64 | 3.55 ± 0.79 | 5.10 ± 0.54 | 4.56 ± 0.26 | 13.32 ± 2.73 | 10.23 ± 0.64 | 10.72 ± 1.49 | 6.98 ± 0.59 |
| During NaCl loading | 4.46 ± 2.20 | 6.08 ± 1.04 | 14.09 ± 1.73 | 20.67 ± 2.66 | 6.41 ± 1.87 | 9.22 ± 2.30 | 7.26 ± 2.04 | 11.89 ± 0.89 | 11.23 ± 1.56 | 11.08 ± 1.13 | 21.70 ± 2.21 | 18.65 ± 3.95 |
| | | | | | | | | | | | | |
| After loading | 4.78 ± 0.79 | 10.42 ± 1.35 | 23.79 ± 1.64 | 48.66 ± 2.58 | 4.95 ± 0.94 | 10.42 ± 1.53 | 4.51 ± 0.47 | 9.03 ± 0.68 | 11.17 ± 1.80 | 14.48 ± 1.69 | 31.03 ± 3.18 | 36.17 ± 6.49 |
| | | | | | | | | | | | | |
| Maximal change | 6.29 ± 2.12 | 13.81 ± 2.85 | 14.10 ± 3.97 | 39.84 ± 4.47 | 4.04 ± 1.91 | 15.81 ± 2.99 | 3.64 ± 2.40 | 12.81 ± 1.53 | -3.30 ± 1.33 | 6.36 ± 1.14 | 23.65 ± 4.00 | 25.47 ± 11.47 |
| | | | | | | | | | | | | |
| p < | 0.05 | 0.05 | 0.01 | 0.001 | NS | 0.005 | NS | 0.001 | 0.05 | 0.02 | 0.001 | 0.05 |

N = four healthy subjects 1 liter 2.9% NaCl during 1 hour M = four healthy subjects 1 liter 2.9% NaCl during 1 hour * = p < 0.05 ** = p < 0.01 *** = p < 0.001

There was a parallel rise in both parameters up to period 9 during and after NaCl infusion. The relationship is expressed by the formula $y = 0.50x + 0.52$ ($r = 0.95$ $p < 0.001$) (Fig 1). The slope of this line was not significantly different from that of the baseline relationship. The relationship between C_{osm} and T_{H_2O} remained constant when C_{osm} was increased either by

prolonged high Na intake or by acute intravenous NaCl loading.

Hypertensive patients (group H) The relationship between C_{osm} and T_{H_2O} is expressed by the formula $y = 0.36x + 0.79$ ($r = 0.82$ $p < 0.001$). The slope of this line was significantly different from that of the baseline relationship ($p < 0.05$). Fig 1) Fractional Cl and K excretion increased to

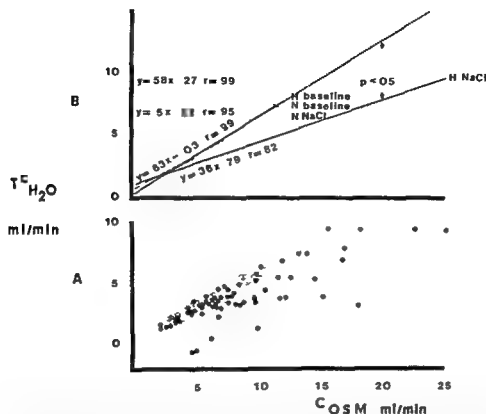


Fig 1 Relationship between C_{OSM} and T_{H_2O} under the influence of a "moderate" intravenous NaCl load in healthy (circles N) and in hypertensive (black dots H) subjects. A All T_{H_2O} values obtained during and after intravenous NaCl loading were plotted against C_{OSM} . B Regression lines of data of baseline and NaCl studies. Note the significant difference between the slopes in the hypertensive group (solid line: baseline extrapolated) vs no difference in the healthy group (dashed line). Asterisk = $p < 0.05$.

rine and blood samples were analyzed for creatinine, sodium, potassium (in all groups), calcium, magnesium, phosphate (in all but group N₁) and uric acid (only in groups N and N₁) by procedures applied to the Technicon Autoanalyzer. Chloride was measured by a chondrometer. All clearances were expressed as a percentage of C_{FR} (creatinine clearance). When calculating Ca and Mg clearances it was assumed* that 60% of the total plasma Ca concentration and 70% of the total Mg concentration underwent ultrafiltration at the glomerulus. Osmolality was determined by an Advanced Osmometer. C_{OSM} and T_{H_2O} were calculated according to standard formulas. In order to save space in the Tables, contracted data of periods 1 and 3 (baseline) to 6 (during NaCl loading) and 7 to 10 (after loading) are included. For unity, period 6 was included in the during NaCl loading; contracted data of Protocols I and II/a. Correlation coefficients and regression lines were computed by the method of least squares. Statistical significance was deter-

mined by the paired t test except when different groups were compared; then the unpaired t test was used. Data are presented as mean \pm SEM.

Results

Baseline relationship between C_{OSM} and T_{H_2O} . A normal relationship between C_{OSM} and T_{H_2O} was established during high NaCl intake by including all baseline values of the healthy subjects (groups N₁ and N) and hypertensive patients (groups H₁ and H). The relationship is expressed by the formula $y = 0.58 \times + 0.27$ ($r = 0.99$, $p < 0.001$) in the healthy subjects and by $y = 0.63 \times - 0.03$ ($r = 0.99$, $p < 0.001$) in the hypertensive patients. No statistical difference was found between the slopes (Fig 1).

Effect of a moderate intravenous NaCl load on the baseline relationship between C_{OSM} and T_{H_2O} .

Healthy subjects (group N₁). The time course of changes in C_{OSM} and T_{H_2O} can be seen in Fig 2.

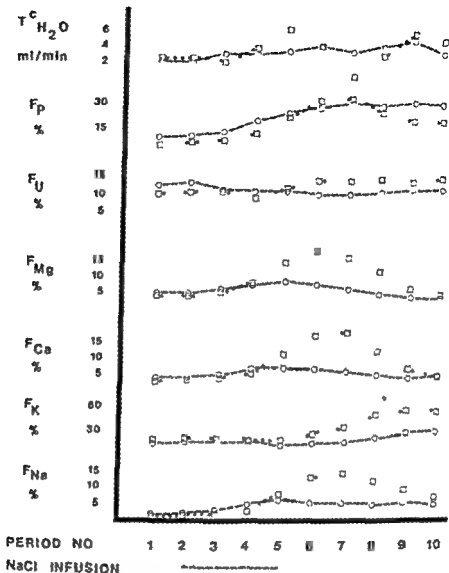


Fig. 4 Time course of changes in fractional excretion of Na, K, Ca, Mg, uric acid (U) and phosphate (P) as well as in T_{H_2O} during and after moderate NaCl loading (circles) and high NaCl loading (squares) $p < 0.005$ $p < 0.01$ $p < 0.005$ $p < 0.001$

NaCl reabsorption in Henle's loop. Our most striking finding was the disruption of the normal correlation between Cosm and T_{H_2O} with some times positive free water clearance values when healthy subjects were infused with high intravenous NaCl loads. Our results are in agreement with those obtained in other studies of the hydrated dog and of human subjects⁹ suggesting that volume expansion inhibits fractional NaCl reabsorption in the distal nephron in a dose related fashion. Depression of the fractional NaCl reabsorption in the distal nephron obviously played a definitive role in the exaggeration of natriuresis when high NaCl loads were given to healthy subjects. The peak fractional Na, Ca and

Mg excretions were simultaneous with the decrease in T_{H_2O} (Fig. 4) also supporting the hypothesis that the reabsorption of interrelated ions⁴ was inhibited in the distal nephron. If fractional phosphate excretion is (within limitations¹⁰) an acceptable proximal marker¹¹ then the lack of difference in phosphaturia between the moderate and high NaCl groups seems to support the distal interpretation (Table II).

An alternative explanation for the observed depression of T_{H_2O} would be insufficient osmotic equilibration in the collecting tubules as a result of excessive osmotic diuretics or/and submaximal ADH effect. This however probably was not the case because osmotic diuresis (Cosm) was not

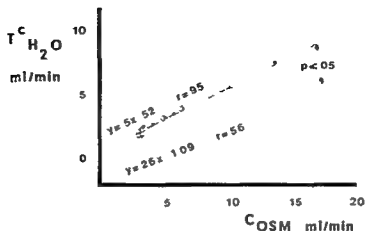


Fig 3 Relationship between C_{OSM} and T_{H_2O} in healthy subjects under the influence of "moderate" NaCl loading (group N, circles) and high NaCl loading (group H, black stars)

significantly higher level in this group than in group N, but there was no significant difference in Na, Ca, Mg and P excretion between the groups (Table I).

Effect of high intravenous NaCl loads on the relationship between C_{OSM} and T_{H_2O} established during moderate NaCl loading

Healthy subjects (group N, Protocol II/a) The relationship during high NaCl loading is expressed by the formula $y = 0.26x + 1.09$ ($r = 0.56$, $p < 0.001$). The slope of this line was significantly different from that of moderate loading ($p < 0.05$). The correlation between C_{OSM} and T_{H_2O} became much less close after a high NaCl load than after a moderate load (Figs 2 and 3). There was a significant difference ($p < 0.001$) between the mean maximum and minimum T_{H_2O} values (6.74 ± 0.48 ml/minute vs 12 ± 0.61 ml/minute) obtained during high NaCl loading but without a significant difference between the corresponding mean C_{OSM} values (17 ± 1.24 ml/minute vs 11.92 ± 1.57 ml/minute) suggesting that the rise of C_{OSM} per se was not responsible for the dramatic decrease in T_{H_2O} (Fig 2). The rises in fractional Na, K, Ca, Mg and Cl excretions were significantly higher after high NaCl loading than after moderate NaCl loading (Table II, Fig 4) but there was no significant difference in P excretions. It is interesting that fractional uric acid excretion slightly decreased after moderate NaCl loading but significantly increased in response to a high NaCl load.

It should be noted that during administration of a relatively high dose of NaCl by slow intrave-

nous infusion (group N, Protocol III) the correlation between changes of C_{OSM} and T_{H_2O} remained excellent ($r = 0.99$, $p < 0.001$).

Hypertensive patients (group H, Protocol II/b) The relationship between C_{OSM} and T_{H_2O} (expressed by the formula $y = 0.27x + 0.59$) was less close after high loading ($r = 0.49$, $p < 0.05$) than after a moderate load in group H ($r = 0.82$, $p < 0.001$). There was a significant difference ($p < 0.001$) between the mean maximum and minimum T_{H_2O} values (5.87 ± 0.43 ml/minute vs 0.86 ± 0.59 ml/minute) but no significant difference was found in the corresponding mean C_{OSM} values (11.09 ± 1.42 ml/minute vs 7.92 ± 1.81 ml/minute).

Discussion

This study clearly shows that acute NaCl loading may depress T_{H_2O} not only in hypertensive patients^{9, 10} but also in healthy subjects (Figs 1 to 3). In earlier studies carried out in dehydrated healthy subjects this has not been reported because during intravenous administration of hypertonic NaCl solutions there was no evidence for an upper limit of T_{H_2O} , as the increasing delivery from the proximal nephron enhanced NaCl transport out of the ascending limb of Henle's loop.⁸ However, in the previous studies only moderate NaCl doses were used¹¹ and the present results show that depression of T_{H_2O} occurred apparently as a dose related consequence of acute NaCl loading. The augmentation of T_{H_2O} at any rate of distal delivery of NaCl was significantly less during high NaCl loading than after moderate NaCl loading suggesting impaired

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when the lowest T_{H_2O} values were measured in the presence of the maximal T_{H_2O} values. Special care was taken to provide the subjects with supramaximal amounts of DDAVP before and during the experiment. The persistence of the correlation between Cosm and T_{H_2O} in group (given not much less NaCl but in slow intravenous infusion) underlined the significance of the speed of acute loading in disruption of the normal relationship.

Our study confirmed that impaired NaCl transport in Henle's loop is a normal renal response to certain degree of volume expansion. In hypertensive persons this response is found even after relatively small NaCl loadings which do not cause any distortion in the normal relationship between Cosm and T_{H_2O} in the healthy subject. Therefore, the impairment in the hypertensives seems not to be due to an intrinsic renal tubular defect but is probably the consequence of a basically normal renal response set to a lower level.

It was concluded that (1) impaired distal NaCl reabsorption may also occur in response to acute NaCl loadings in the dehydrated healthy subject and (2) EN is a normal renal response abnormally set to a lower level in the hypertensive patient.

Summary

The effects of graded acute intravenous hypertonic NaCl loads on the baseline relationship between osmolal clearance and free water reabsorption established during high NaCl dietary intake and on the fractional excretion of various electrolytes were investigated in 15 healthy subjects and 12 normal renin essential hypertensive patients. No significant influence on the baseline relationship could be demonstrated after a moderate NaCl load in the healthy subjects while the water reabsorption was depressed by the same intervention in the hypertensive patients. High NaCl loads induced depression of free water reabsorption in a dose related fashion in both groups. No difference was found in phosphaturia between the groups after the same NaCl load as well as in the healthy persons after different NaCl loads supporting the contention that the observed differences in free water reabsorption are not due to changes in the proximal nephron. It was concluded that (1) impaired NaCl reabsorption in Henle's loop (depression of free water reabsorption) may also occur in response to acute

NaCl loadings in healthy subjects and (2) exaggerated natriuresis is the consequence of a normal renal response (impaired NaCl transport in Henle's loop) to a certain degree of volume expansion reset abnormally to a lower level in hypertensive patients.

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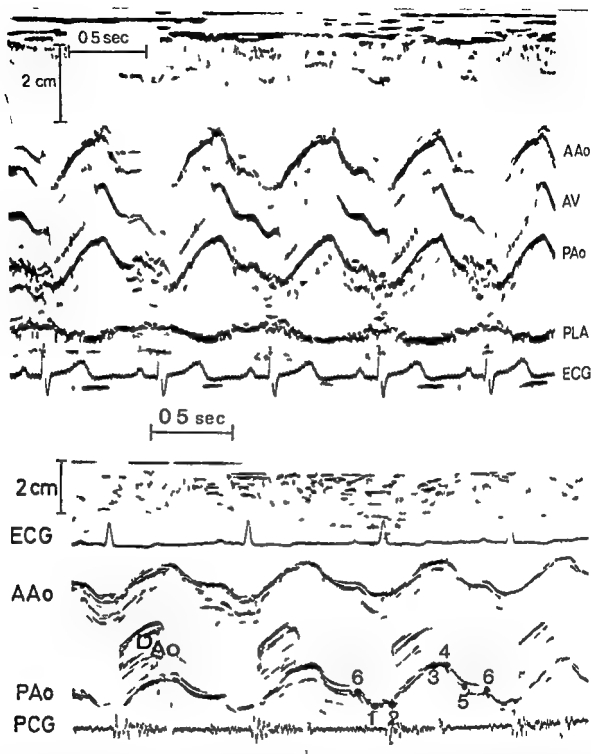


Fig 1 *a* (upper panel) Echogram of the aortic root of a healthy ten year old child. Note the typical box like systolic configuration of the aortic cusps. In diastole the cusps produce a midline echo configuration (AV). Closure of the aortic cusps has already taken place before the dorsally directed motion of the aortic root begins. Note the synchronous dorsally directed motion of the posterior left atrial wall (PLA) accompanying ventrally directed motion of the aortic root and the resultant increase in the diameter of the left atrium. *b* (lower panel) Echograms of the aortic root of a 26 year old man with a tilting Bjork Shiley valve prosthesis. 1 to 6 are characteristic points in the cyclical aortic root configuration (for detail see text). ECG-electrocardiograms. AAo and PAo = anterior and posterior view of the aortic root. DA = tilting disc of the Bjork Shiley valve in the opened position. PCG = phonocardiograms taken right parasternally in the second intercostal space.

Echocardiographic pattern of motion of the aortic root as a correlate of left atrial volume changes*

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The pattern of motion of the aortic root is characterized by parallel movement of its anterior and posterior walls and is usually simple to record echocardiographically. The distance between the two walls as a correlate of the diameter of this vascular structure^{1,2} and evaluations of the aortic leaflet motion between the two dominant echoes³⁻⁵ have been the subject of several investigations. Recently attempts have been made to correlate the typical systolic motion of the aortic root in the direction of the anterior wall of the thorax with the stroke volume of the left ventricle.⁶

When recording the echoes of normal aortic leaflets and particularly during postoperative studies of Björk Shiley aortic valve prostheses⁷ it was noted that the systolic motion of the aortic root towards the anterior thorax wall uniformly continues beyond closure of the valve. This finding indicates that a direct correlation between stroke volume of the left ventricle and systolic aortic root motion is doubtful.

In this study we have therefore attempted to correlate the motion of the aortic root with further echocardiographically detectable struc-

tures and with the ECG, the PCG, the carotid pulse curve or the apexcardiogram as well. The results indicate that the echocardiographically detectable motion of the aortic root is not caused by the volume ejected into the aorta during systole but is an index of changes in volume of the left atrium.⁸

Similar conclusions have been reported by Strunk and associates⁹ in recent studies comparing hemodynamic and cineangiographic findings with the simultaneously recorded echocardiographic pattern of the posterior aortic wall.

Material and method

Forty-eight male and 34 female patients aged between 10 and 68 years (average age 54 years) were studied. In 32 cases the studies were performed during routine examinations after implantation of aortic and/or mitral valve prostheses (Björk Shiley tilting disc valve). There were no clinical or echocardiographic signs of malfunction of the prostheses. The prostheses in the aortic position were implanted with a standardized operative procedure in such a way that the asymmetric strut was positioned left anteriorly between the two coronary ostia. In consequence the disc opening movement turned in a left anterior direction toward the ultrasonic beam. In the mitral position the strut of the prostheses was placed so that the protodiastolic major disc pivoted toward the aortic outflow tract in the direction of the septum and, thus, also in a ventral direction toward the transducer.¹⁰ In the remaining 60 cases there was no sign of an aortic or mitral defect.

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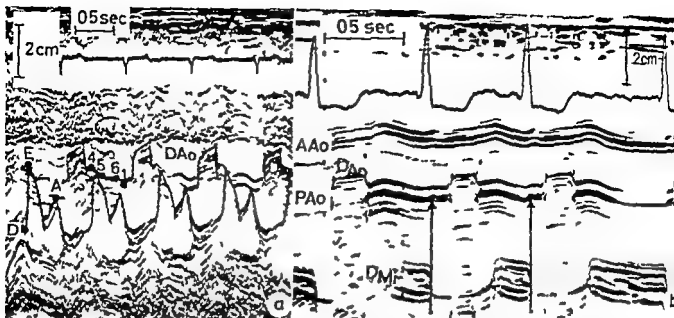


Fig 3 a On simultaneous registration of the posterior walls of the aortic root and of the tilting disc of the valve prosthesis (D_A) and of the anterior mitral leaflet ($D E A$) it can be clearly seen (1) that Point 4 in aortic root motion is concomitant with the opening slope $D E$ and (2) that the posterior movement of the aortic root from Point 6 to Point 1 corresponds to the A wave b This echogram records the tilting discs of the aortic (D_A) and mitral valve (D_M) prosthesis Due to atrial fibrillation the dorsally directed motion from 6 to 1 is absent Note the small notch in the aortic root motion at the beginning of the isometric ventricular contraction (+)

The echocardiographic examinations were carried out with a scope display echocardiograph unit manufactured by Organon Teknika with a Polaroid camera and Honeywell strip chart recorder with chart speeds of 25, 50, and 100 mm/sec. The ultrasound frequency was 2.25 MHz. The transducer was placed in the second to fifth intercostal space (usually the third or fourth) 2 to 5 cm left parasternal. A complete sector scan was made by the usual method and individual structures in differing intercostal spaces were separately recorded with the patients lying on their backs and the trunk elevated to approximately 30 degrees.

ECGs and in most cases PCGs were simultaneously recorded routinely at the second left intercostal space parasternally. Apexcardiograms or carotid pulse curves were also obtained.

The results reported in this study were found to be reproducible by different examiners and independent of age and sex of the patients.

Results

During sinus rhythm six points in the parallel echo curves of the anterior and posterior walls of the aortic root can be regularly identified in patients with aortic valve prostheses (see Fig 1b).

In contrast in patients with normal aortic valves it is frequently impossible to determine Points 2 and 3—opening and closing of the aortic valve—with accuracy. This accounts for the impression that there is a correlation between the time course of the ventral movement of the aortic root and the mechanical systole of the left ventricle. The two representative examples in Fig 1 show that the motion of the aortic root in the direction of the anterior thorax wall definitely continues beyond closure of the valve. It is also clear that the posteriorly directed aortic root motion does not begin (Point 4) until after the second heart sound. The steepest part of the aortic root curve is that between Points 4 and 5; thereafter a plateauing occurs. At Point 6 (immediately after the P wave in the ECG) the aortic root accelerates again in the direction of the posterior chest wall until Point 1 is reached. The course of the curve between Points 1 and 2 is practically horizontal whereby a small wave can occasionally be noted concomitantly with sets 1 and 2 of the first heart sound (mainly at the posterior wall of the aortic root).

The objective was thus to correlate the motion of the aortic root not only with the ECG and the PCG but also with the carotid pulse curve (CP), the apexcardiogram (ACG) and the echocardi-

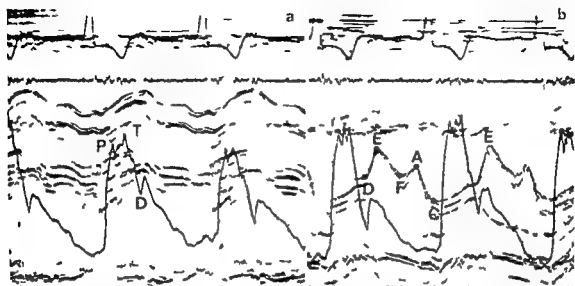


Fig 2 a and b ECG and PCG tracings (right parasternal second intercostal space) a echogram of the aortic root and b echogram of the anterior mitral valve leaflet recorded simultaneously with the carotid pulse curve P = percussion wave T = tidal wave D = dicrotic notch For details see text

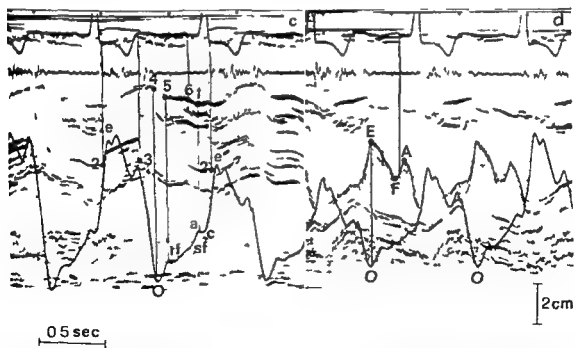


Fig 2 c and d ECG and PCG tracings (right parasternal second intercostal space) c echogram of the aortic root and d echogram of the anterior mitral valve leaflet recorded simultaneously with the apexcardiogram c = beginning of left ventricular contraction e = beginning of left ventricular ejection period O = mitral valve opening time rf = rapid filling wave sf = slow filling wave a = wave in response to atrial contraction For details, see text

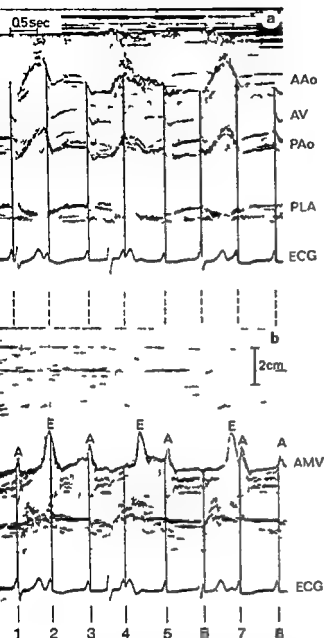


Fig 5 The influence of contraction of the left atrium (complete AV block) on the echographic pattern of the aortic root (a) and the anterior mitral leaflet (b) See text for details.

2 Point 5 indicates the end of the rapid filling phase

3 The posteriorly directed acceleration from Point 6 to Point 1 can only be clearly identified in patients with sinus rhythm (compare Figs 3a and 3b)

Fig 3b also shows that the small wave between Points 1 and 2 of the aortic root movement occurs during the isovolumetric phase of the left ventricle as the mitral valve has already closed at this point and the aortic valve has not yet been opened by the pressure rise in the left ventricle. Final proof that the dorsal acceleration of the

aortic root curve from Point 6 to Point 1 is only an expression of a change in volume in the left atrium after its contraction is supplied by Fig 4. A sinus rhythm prevails in the case of this patient with a Bjork Shiley prosthesis. Each P wave (vertical lines) is followed by the previously mentioned dorsally directed motion of the aortic root. When a supraventricular extrasystole without atrial excitation occurs there is no dorsal displacement from Point 6 to Point 1. Also remarkable is the fact that a slow motion of the aortic root toward the anterior chest wall can be observed during the compensatory pause after the supraventricular extrasystole. This finding is completely contrary to a hypothetical correlation between the ejection volume of the left ventricle and the ventral motion of the aortic root.

The results previously obtained have included the finding that both walls of the aortic root are subject to presystolic dorsally directed motion apparently as a consequence of the contraction and the associated active emptying of the left atrium. This would indicate that motion of the posterior wall of the aortic root is consistent with its anatomical juxtaposition and is due to the dorsally directed contraction of the anterior atrial wall counterpart of the simultaneous ventrally directed motion of the posterior wall of the left atrium (see Fig 1a). Consequently the parallel movement of the anterior wall of the aortic root should be regarded as purely passive. If this hypothesis is correct changes in the volume of the left atrium will then influence the pattern of motion of the aortic root independently of the course of ventricular contraction.

In order to investigate this possibility patients with complete AV blocks were echocardiographically examined. Sections from a continuous echocardiogram of the aortic root (Fig 5a) and the mitral valve (Fig 5b) from each patient were superimposed in order to demonstrate the influence of atrial contraction on these two structures and to correlate timing. As can be seen in Fig 5b an opening movement of the mitral valve (correlated with P waves No 1 3 5 7 8) or a change in the configuration of the E wave (P wave No 2) corresponds with each excitation and subsequent atrial contraction during the ventricular diastole. If atrial contraction occurs during the ventricular systole however recognition of this finding in the pattern of motion of the mitral valve (P waves No 4 and 6) is precluded.

On the other hand each contraction of the

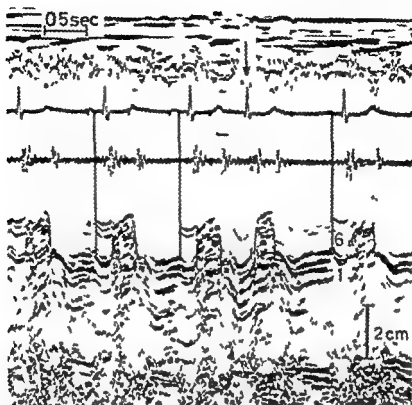


Fig 4 The typical posterior motion of the aortic root from Point 6 to Point 1 is noted at the end of each P wave this is absent in the case of a supraventricular extrasystole (†) without atrial excitation

graphic movements of the mitral valve (Fig 2) A comparison of the time course of aortic root motion with the simultaneously recorded carotid pulse curve (Fig 2a) demonstrates that the characteristics of the two curves do not coincide at any time Two observations are of particular interest

1 Taking pulse wave speed into account it can be seen that at the time of the percussion wave (P) in the CP curve motion of the aortic root in the ventral direction has just begun

2 The ventral motion of the aortic root continues with the same slope even after the tidal wave (T) in the CP curve

Shortly after the second heart sound and the dirotic notch (D) in the CP curve the aortic root begins to move toward the posterior chest wall (Point 4) Thus Point 4 would therefore appear to correspond with the opening motion (D E) of the mitral valve (Fig 2b) and to be directly before the H point of the ACG (Fig 2c) Fig 2c clearly shows that interruption of the steep movement of the aortic root toward the posterior chest wall (Point 5) coincides with the end of the rapid filling phase (rf) in the apexcardiogram The flat section of the

aortic root curve from Point 5 to Point 6 reflects the slow filling phase (sf) of the ACG Point 6 then corresponds temporally with the end of the P wave in the ECG and with the beginning of the A wave of the anterior mitral leaflet (Fig 2d) The following aortic root motion toward the posterior chest wall is accompanied by contraction of the atrium The end of this coincides with the a wave in the ACG and with Point 1 of the aortic root curve In view of the coincidence of timing with the c point in the ACG the small wave at the posterior aortic root wall and before opening of the valve probably represents the isovolumetric course of contraction of the left ventricle in the echocardiogram

In a number of patients aortic and mitral valve motion was simultaneously recorded

In Fig 3a the aortic root motion was clearly identified in a patient with an aortic valve prosthesis and a normal mitral valve and in Fig 3b it was identified in a patient with both aortic and mitral valve prostheses

The tracings show

1 Point 4 coincides exactly with the opening movement of the mitral valve (DE)

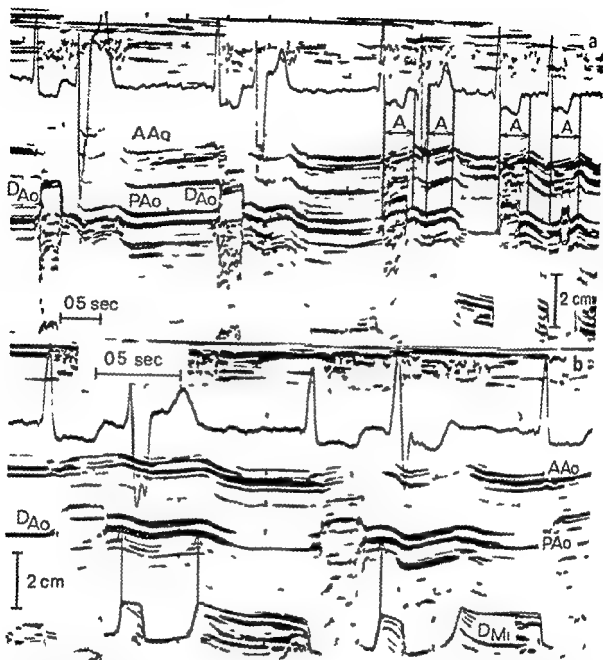


Fig 8 Echograms of the aortic root of a patient with a Bjork Shiley prosthesis in the aortic and mitral positions with atrial fibrillation and ventricular extrasystoles. The early extrasystoles cause mitral valve closure but do not induce opening of the aortic valve (b). In spite of this the diastolic motion of the aortic valve is ventrally directed even after an extrasystole (a and b). The duration of this movement (A) is only slightly influenced by the left ventricular ejection period (a). b again shows that the diastolic posterior motion of the aortic root does not take place until after the mitral valve has opened (†).

sequently, the following, clearly recognizable ventral displacement of the aortic root cannot be taken as an index of a displacement of volume from the ventricle to the aorta. As can be seen at the right hand edge of Fig 8a, the ventrally directed motion of the aortic root also appears to be little influenced in its amplitude and duration

by the duration of aortic valve opening and by the ejection period of the left ventricle respectively.

On the other hand this anterior aortic motion cannot represent the retrograde flow in the left atrium, since the mitral valve is closed immediately on occurrence of the extrasystole as a result of the induced pressure rise in the left ventricle.

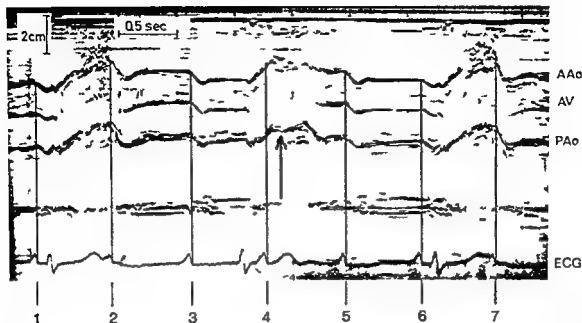


Fig 5 Echocardiographic pattern of the aortic root (AAo = anterior wall PAo = posterior wall of the aortic root AV = aortic valve) of a patient with a complete AV block Note (↑) the interruption of ventral movement of the aortic root caused by atrial contraction Each following atrial contraction also influences the pattern of aortic motion.

atrium causes dorsally directed motion of the aortic root (P waves Nos 1 3 5 6 8) or acceleration of such motion (P waves Nos 2 7) regardless of the phase of ventricular excitation or contraction in which it occurs as is clearly shown by Fig 5a The echocardiographic pattern of the aortic root motion after the P wave No 4 in Fig 5a and Fig 6 also makes it apparent that atrial contraction can even interrupt the ventrally directed motion of the aortic root

The complete independence of the aortic root motion from the systolic ejection of the left ventricle into the aorta could be definitively demonstrated in a patient with a Björk Shiley prosthesis and complete AV block (Fig 7) at the opening of the prosthetic disc the time of maximal flow in the aorta the aortic root does not move anteriorly but dorsally if atrial contraction occurs concomitantly (P waves No 1 and 3)

Finally Fig 5a (like Fig 1) also clearly shows that the anterior movement of the aortic root correlates with a flatter dorsally directed motion of the posterior wall of the left atrium This finding reflects the expected increase in volume of the left atrium during the ventricular systole

After having shown that a quantitative correlation between the effective systolic volume ejected by the left ventricle and the aortic root motion does not exist the influence of the ventricular

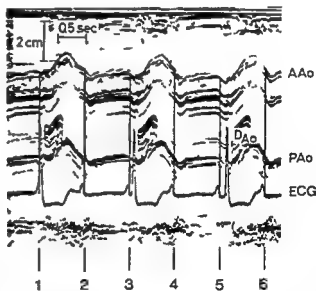


Fig 7 Echocardiograms of the aortic root of a patient with a Björk Shiley aortic valve prosthesis and complete AV block The aortic root motion is dorsally directed after the P waves 1 and 3 although the aortic valve has already been opened by ventricular contraction.

systole on the echo pattern of the aortic root was examined

The echocardiograms of patients with ventricular extrasystoles (Fig 8a) demonstrate that the aortic valve (in this case prosthetic) does not open at all if the extrasystole occurs early Con

Decisive for our interpretation namely that there is no direct correlation between antegrade ejection and ventral aortic root motion are the findings which show the existence of such a motion after extrasystolic ventricular contraction *without* opening of the aortic valve (Fig. 8) and on the other hand a dorsally directed movement of the aortic root when the aortic valve is already open in the case of coincidence of ventricular and atrial systoles (Figs. 6 and 7)

In view of these findings the claim of Pratt and colleagues⁸ that aortic root motion can be taken as an index of stroke volume is no longer tenable. If changes in the amplitude of aortic root motion are to be taken as correlates of stroke volume (to be exact changes in the volume of left atrium) at all they can only be evaluated when it is certain that neither size nor compliance of the left atrium change. This would in turn mean that the amplitude of aortic root motion can only be regarded as a sensitive parameter for assessing the ejection capacity of the left ventricle in acute experiments and with patients *without* mitral insufficiency or atrial septal defect.

Summary

The movement of the aortic root under resting conditions was analyzed echographically in 82 patients (32 were postoperative examinations of Bjork Shiley aortic and/or mitral valve prostheses). Additionally ECG PCG carotid pulse curve or spexcardiogram were recorded simultaneously in the majority of the cases. In view of the time correlation between these noninvasive parameters the results clearly show that both ventrally and dorsally directed motions of the aortic root during the cardiac cycle only reflect the change in volume of the left atrium. Thus

aortic root motion might if at all be an indirect index of left ventricular stroke volume and/or so if sinus rhythm is present and no mitral insufficiency or atrial septum defect exist.

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(Fig 8b) The ventral motion of the aortic root probably reflects only the antegrade pressure passive flow from the pulmonary system into the left atrium

Discussion

It has been reported that the two dominant echoes comprising the root of the aorta are probably the easiest of all cardiac echoes to record. However, this statement is contradicted by the lack of studies on the pattern of motion on this vascular structure which is automatically recorded echocardiographically in the course of assessing the functioning of aortic valves. The cyclical motion of the aortic root was subdivided simply into a systolic movement towards the anterior thorax wall and a diastolic dorsally directed movement. The cause of this motion was thought to be the course of contraction of the left ventricle either in the sense of a possible centrifugal effect or as the consequence of the effective antegrade ejected volume.¹ Only the presystolic dorsally directed motion of both walls of the aortic root for example as shown in Figs 1 and 3 was attributed to the contraction of the left atrium since it is absent in the presence of atrial fibrillation.⁴

The finding that the ventrally directed motion of the aortic root always continued beyond valve closure has been reported but not discussed in several papers.^{1,4,6} The lack of interpretation of this phenomenon may be due to the fact that the opening and closing motions of the aortic valve can only be recorded exactly in about 30% of normal cases and that multiple scarcely analyzable echoes between the aortic root limits are registered⁸ in the case of diseased aortic valves particularly when stenosis is present.

Confirming the conclusions of Strunk and associates¹² the results of our study clearly show that the diastolic pattern of the aortic root in the echogram corresponds exactly with the time course of the physiological changes in volume of the left atrium (Figs 2, 3, 4 and 5). The dorsally directed motion of the aortic root (Point 4) does not begin simultaneously with closure of the aortic valve (Point 3) but always begins with the DE slope of the anterior mitral leaflet. This initially relatively steep motion flattens out (Point 5) at the end of the rapid filling phase of the left ventricle (rf) and then demonstrates repeated acceleration (Point 6) in concomitance

with the A wave of the anterior mitral leaflet i.e. through atrial contraction finally reaching the lowest point Point 1. If atrial fibrillation occurs the acceleration wave from Point 6 to 1 is absent.

The motion of the anterior aortic root wall which is parallel to the posterior must therefore be regarded as passive transmission of the motion of the anterior left atrial wall via the posterior aortic wall. The reported larger amplitude of the maximal excursion of the anterior wall probably has no relation to an asymmetrical extension of the aortic wall during the ejection period but may be only the result of an oblique echo path and thus the expression of differing projections. In this regard it is significant that no marked differences in the diameter of the aorta were detected throughout the entire cardiac cycle.

If the entire diastolic motion of the aortic root is apparently correlated with the process of emptying of the left atrium into the left ventricle one must discuss to what extent the anterior systolic motion of the aortic root is also the expression of a change in volume of the left atrium in the sense of an increase in volume as physiologically expected during the left ventricular systole. The primary finding in favor of this hypothesis is that the ventral motion of the aortic root is accompanied by a dorsally directed motion of the posterior wall of the left atrium which although not so pronounced can frequently still be clearly determined echographically (Figs 1a and 5a). Several of the findings presented in this study do not support the assertion that there may be a direct quantitative correlation between the stroke volume of the left ventricle and the amplitude and duration of the ventral motion of the aortic root.⁸ Even a comparison of the course of the carotid pulse curve or the apexcardiogram with the echocardiographic pattern of aortic root motion (Figs 2a and 2b) does not support the thesis that the stroke volume influences the movement of this vascular structure. The tracing representing the ventral movement of the aortic root rises in fact constantly during the ejection period independently of the maximal aortic flow and volume changes expected during the upstroke of the carotid pulse curve to the percussion wave or to the c wave in the apexcardiogram. The slope of the aortic root motion curve declines only slightly when the aortic valve has closed.

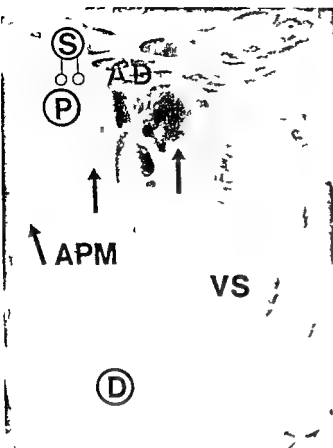


Fig 1 Photograph of an infarcted tissue preparation dissected from the left ventricle of a dog 24 hours after ligation of the left anterior descending coronary artery. Arrows indicate the demarcation between normal tissue *above* which appears dark and infarcted tissue *below* which appears pale VS indicates the ventricular septum APM is the anterior papillary muscle and AD is the anterior division of the left bundle branch which is a free running false tendon P and D indicate the approximate locations of the proximal and distal recording sites respectively and the position of the extracellular stimulating electrodes is indicated by S

reductions of resting membrane potential and of action potential amplitude and maximum velocity of phase 0 depolarization Action potential duration was increased as was the duration of the refractory period Impulses propagating in infarcted regions exhibited slowing of conduction and unidirectional block and reentry were demonstrated Enhanced automaticity was also observed It was postulated that these abnormal electrophysiological properties might form the basis of at least some of the ventricular arrhythmias which commonly complicate acute myocardial infarction

The effects of a drug lidocaine on the abnor

mal Purkinje fibers surviving in infarcted regions were subsequently studied by Allen and colleagues²¹ who found that the drug's effects on such cells were different from what would have been predicted based on knowledge of its effects on normal cells Other investigators using a variety of drugs on cardiac tissues depressed by means other than acute myocardial infarction have also found that abnormal tissues may respond to drugs differently than do normal tissues^{2, 22}

It is conceivable therefore that the abnormal Purkinje fibers surviving in infarcted regions might respond to digitalis differently than do normal fibers and that patients or animals with acute myocardial infarction might be susceptible to toxic arrhythmias on this basis In the present study we have tested this hypothesis using microelectrode techniques *in vitro* on tissue preparations obtained from infarcted canine hearts identical to those used by Friedman and Allen and their co workers^{17, 18, 23}

Methods

Myocardial infarction was produced in previously healthy adult mongrel dogs weighing 10 to 15 kilograms by ligating the left anterior descending artery under general anesthesia with intravenous sodium pentobarbital (30 mg/kg) using previously described techniques¹⁷ The animals were allowed to recover from the anesthesia and then approximately 24 hours later the survivors were reanesthetized with sodium pentobarbital (15 to 30 mg/kg) and the hearts were rapidly excised and dissected in cooled oxygenated Tyrode's solution the composition of which has been described previously¹ The portion of the left ventricle comprising the anterior half of the interventricular septum and the paraseptal free wall with attached anterior papillary muscle was dissected free of other tissue and was pinned endocardial surface up to the wax base of a tissue bath (volume 50 ml) and superfused with Tyrode's solution at 20 ml/minute The dissection procedure has been described in detail elsewhere¹⁷ The apical half to two thirds of the tissue preparations was infarcted but the basal portion including the tip of the anterior papillary muscle and the attached anterior division of the left bundle branch was invariably spared (Fig 1) Differentiation between normal and infarcted tissue was easily accomplished by gross inspection

Effects of ouabain on the electrophysiological properties of subendocardial Purkinje fibers surviving in regions of acute myocardial infarction

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The belief that patients with acute myocardial infarction have enhanced susceptibility to the toxic effects of digitalis is widespread and is based primarily on animal studies which have consistently demonstrated that toxic arrhythmias develop at lower doses of digitalis in animals with experimental acute myocardial infarction than in normal animals.¹ The clinical evidence supporting this concept is anecdotal and tenuous however^{2,3} and there have been several clinical studies in which no evidence of enhanced toxicity of digitalis in patients with acute myocardial infarction was found.⁴⁻¹⁰ Nevertheless recent review articles and widely used current reference sources continue to indicate that patients with acute myocardial infarction have enhanced susceptibility to the toxic arrhythmias of digitalis.¹¹

The electrophysiological mechanisms responsible for arrhythmias occurring as a complication of digitalis toxicity have been extensively investigated using microelectrode techniques (for Reviews see references 14 and 15). A study carried out by Rosen and co workers¹⁶ is of particular interest since it correlated *in vivo* electrocardiographic evidence of digitalis toxicity with *in vitro* intracellular microelectrode recordings using an experimental preparation in which Purkinje

fibers excised from a dog's heart were perfused in a tissue bath with blood from a living donor dog. They demonstrated that the appearance of toxic arrhythmias in the donor dog's heart during ouabain infusion was associated with decreases in action potential amplitude, resting membrane potential, maximum rate of phase II depolarization and action potential duration of the simultaneously recorded Purkinje fiber transmembrane potentials and slowing of conduction velocity. In some experiments automaticity due to phase 4 depolarization was enhanced. In others automaticity was enhanced due to the occurrence of oscillatory afterpotentials (which Rosen and associates referred to as low amplitude potentials). Such oscillatory afterpotentials have also been observed by many other investigators in recent years and are now believed to play an important role in the genesis of digitalis arrhythmias.¹⁷⁻¹⁹

Most of the investigation into the cellular electrophysiological correlates of digitalis toxicity including the work of Rosen and associates cited above has been conducted on normal cardiac tissues. In acute myocardial infarction however cellular electrophysiological properties are altered by the disease process. The alterations which occur during the most acute phases of infarction are poorly understood at present but those which persist beyond 24 hours have been studied in detail.²⁰ Friedman and co workers²¹⁻²³ found that canine subendocardial Purkinje fibers surviving in infarcted regions 24 to 72 hours after coronary artery ligation exhibited

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Table 1 Effects of ouabain on transmembrane resting and action potential characteristics

| | Proximal site | | | Distal site | | |
|----------------------------------|---------------------|------------------------|----------------|---------------------|------------------------|-------|
| | Normal preparations | Infarcted preparations | I ₁ | Normal preparations | Infarcted preparations | P |
| MDP (mV) | | | | | | |
| Control | 83.0 ± 1.5 | 83.6 ± 1.1 | NS | 88.0 ± 1.7 | 78.6 ± 2.7 | <0.05 |
| Ouabain 2.5 × 10 ⁻⁶ M | 82.5 ± 1.8 | 82.9 ± 0.8 | NS | 83.4 ± 2.3 | 77.5 ± 2.0 | NS |
| P ₁ | NS | NS | | NS | NS | |
| Amp (mV) | | | | | | |
| Control | 121.5 ± 2.5 | 118.8 ± 1.7 | NS | 122.6 ± 2.6 | 117.2 ± 4.9 | NS |
| Ouabain 2.5 × 10 ⁻⁶ M | 118.3 ± 2.7 | 114.2 ± 4.4 | NS | 121.3 ± 4.0 | 107.5 ± 4.4 | NS |
| P ₁ | NS | NS | | NS | NS | |
| V _m (V/sec) | | | | | | |
| Control | 403.3 ± 31.4 | 449.2 ± 22.5 | NS | 419.0 ± 34.7 | 342.2 ± 43.2 | NS |
| Ouabain 2.5 × 10 ⁻⁶ M | 497.7 ± 70.8 | 437.0 ± 46.8 | NS | 446.2 ± 91.9 | 373.3 ± 34.9 | NS |
| P | NS | NS | | NS | NS | |
| MD (msec) | | | | | | |
| Control | 237.8 ± 16.7 | 219.3 ± 7.9 | NS | 211.4 ± 15.5 | 227.4 ± 11.3 | NS |
| Ouabain 2.5 × 10 ⁻⁶ M | 222.2 ± 9.0 | 212.3 ± 11.6 | NS | 201.8 ± 9.3 | 236.1 ± 16.2 | NS |
| P | NS | NS | | NS | NS | |
| APD (msec) | | | | | | |
| Control | 348.8 ± 16.2 | 374.0 ± 9.2 | NS | 331.4 ± 20.8 | 431.2 ± 21.0 | <0.05 |
| Ouabain 2.5 × 10 ⁻⁶ M | 362.2 ± 15.4 | 397.3 ± 1.7 | NS | 338.2 ± 16.0 | 467.5 ± 21.3 | <0.01 |
| P | NS | NS | | NS | <0.01 | |

All values are mean ± SEM obtained from five normal preparations and eight infarcted preparations. P indicates the significance of the difference between mean control values and mean values obtained during exposure to ouabain 2.5 × 10⁻⁶ M while I₁ indicates the significance of the difference between the mean values obtained at a given site in normal preparations and the mean values at the same site in infarcted preparations. MDI = maximum diastolic potential; Amp = action potential amplitude; V_m = maximum rate of depolarization of phase 0; APD = action potential duration to 50% and 100% repolarization respectively.

by measuring the distance between the onset of the action potential upstrokes at the two sites. Then with the transmembrane potentials being recorded continuously on moving film premature stimuli were introduced at progressively shorter coupling intervals after every eighth basic drive stimulus. The intervals between the responses to the basic drive and premature stimuli at the proximal site (P₁P₁) and the distal site (D₁D₁) were determined until excitation of the subendocardial Purkinje fibers at the proximal site failed due to absolute refractoriness of those cells. The effective refractory period was defined as the shortest P₁P₁ interval at which conduction to the distal site was successful while the functional refractory period was the shortest D₁D₁ interval achieved. The absolute refractory period of the cells at the proximal site was the minimum P₁P₁ interval achieved.

In some experiments as the coupling interval of basic and premature stimuli (SS) was decreased the P₁P₁ interval decreased *pari passu* up to a point then increased. Because of the very short distance between the stimulating electrode

pair and the microelectrode at the proximal recording site we felt it was unlikely that the phenomenon was due to conduction delay between the stimulating and proximal recording sites but was probably due to indirect activation of the Purkinje fibers at the proximal site via the underlying muscle P₁P₁ and D₁D₁ interval recorded under such circumstances were discarded. In those experiments the effective refractory period was still the shortest P₁P₁ interval at which conduction occurred to the distal site but the functional refractory period was the shortest D₁D₁ interval achieved before latency developed between the stimulating and proximal recording sites.

3 Spontaneous activity While transmembrane potential was being simultaneously recorded from subendocardial Purkinje fibers at both the proximal and distal sites the basic drive stimuli were abruptly terminated for approximately 10 seconds. The occurrence of spontaneous action potentials during the interruption of driving stimuli was noted if it occurred and the sequence of activation at the proximal and distal

tion—a method which has been validated by others.¹¹ For control studies anatomicallly identical tissue preparations were prepared from the hearts of normal dogs.

The superfusate was equilibrated with 95% O₂, 5% CO₂ and maintained at a temperature of $36 \pm 1^\circ \text{C}$. Its potassium concentration was 4.0 mM in all experiments.

All preparations were stimulated extracellularly at a cycle length of 800 msec via Teflon insulated bipolar silver electrodes located on the non infarcted tip of the anterior papillary muscle. Basic drive stimuli (S_1) were rectangular pulses 2 to 3 msec in duration and 1 to 2 times diastolic threshold in amplitude. For experiments in which conduction of premature beats and refractory periods were measured, premature impulses were delivered via the same electrode pair at selected intervals after S_1 . The premature stimuli (S_2) were rectangular pulses 2 to 3 msec in duration and >5 times diastolic threshold. All stimuli were isolated from ground. Transmembrane potentials were recorded through glass microelectrodes filled with 3 M KCl with tip resistances of 10 to 20 megohms. The microelectrodes were coupled via a silver silver chloride electrode to a preamplifier with high input impedance (1.5×10^{11} ohms) and capacitance neutralization.¹² The output of this preamplifier was displayed on oscilloscopes (Tektronix models 5433 and 5103N) and was photographed with oscilloscopic cameras (Grass model C4 and Tektronix model C5A respectively). The maximum rate of depolarization of action potentials was determined by electronic differentiation as described by Bigger and co workers.¹³

In all experiments subendocardial Purkinje fibers were impaled at two sites: a proximal one on the tip of the papillary muscle within 1 mm of the insertion of the false tendon carrying the anterior division of the left bundle branch and a distal site on the apical portion of the preparation below the insertion of the papillary muscle (Fig. 1). In all preparations the proximal site was within 2 mm of the stimulating electrode pair and was in normal tissue even in the tissue preparations with infarcts. The distal site was well within the infarcted region in infarcted tissue preparations whereas in the non infarcted preparations it was of course in normal tissue. All

control observations were made after an equilibration period of at least 2 hours following dissection and mounting and during which the tissue preparation was driven regularly at a cycle length of 800 msec and was superfused as described above. Ouabain was then added to the superfusate in a concentration of 2.5×10^{-6} M and observations were repeated after exposure to the drug for between 90 and 120 minutes. The concentration of ouabain was lower than generally used in studies of toxicity. Preliminary experiments however had shown that conventional toxic doses of the drug caused the tissue preparations to rapidly develop spontaneous activity to such a degree that it was impossible to drive the tissue regularly and so to repeat during drug exposure the protocol which had been followed in the control period. By trial and error a dose was selected which caused toxic manifestations to develop sufficiently slowly so that this problem was circumvented.

The experimental observations fell into three categories:

1 *Transmembrane resting and action potential characteristics.* Between five and 10 subendocardial Purkinje fibers were impaled consecutively at both the proximal and distal sites and photographic records were made of the transmembrane resting and action potential characteristics of each cell. At the two sites all impalements were made within a 1 sq mm area. This procedure was repeated during exposure to ouabain. Data obtained from individual cells was pooled to give average values of the various transmembrane potential parameters for the two sites under control conditions and during drug exposure. These averaged data were then subjected to statistical analysis. It was necessary to make multiple impalements and use averaged data for analysis because movement of the tissue preparations particularly during exposure to ouabain rendered it impossible to maintain continuous impalements of single cells.

2 *Refractoriness and conduction.* Two cells were impaled simultaneously, one at each site. The two transmembrane potential recordings were displayed simultaneously on an oscilloscope. With the tissue being driven at a constant cycle length of 800 msec, photographs were made of the simultaneously displayed action potential upstrokes recorded at a rapid sweep speed (1 cm/5 msec). Conduction time was determined

Table II Effects of ouabain on conduction and refractoriness

| | Conduction time | | Absolute refractory period (proximal site) | | Effective refractory period | | Functional refractory period | |
|------------------------|-----------------|-----------------------------------|---|-----------------------------------|-----------------------------|-----------------------------------|------------------------------|-----------------------------------|
| | Control | Ouabain 2.5×10^{-6} M | Control | Ouabain 2.5×10^{-6} M | Control | Ouabain 2.5×10^{-6} M | Control | Ouabain 2.5×10^{-6} M |
| Normal preparations | 812 ± 12 | 72 ± 13 | 297.5 ± 20.6 | 310 ± 23.5 | 297.5 ± 20.6 | 310 ± 23.5 | 297.5 ± 18.9 | 315 ± 19.4 |
| Infarcted preparations | 140 ± 16 | 103 ± 14 | 311.7 ± 16.6 | 331.7 ± 12.8 | 333.2 ± 12.3 | 338.3 ± 11.7 | 356.7 ± 20.4 | 351.7 ± 19.7 |
| P | < 0.05 | NS | NS | NS | NS | NS | NS | NS |

All values are mean \pm SEM expressed in millisecond. Results were obtained from experiments in 11 normal preparations, in 10 infarcted preparations. Conduction time was measured in 10 experiments and refractory periods in six. The significance of the difference in mean values for a given parameter between normal and infarcted preparations is indicated by P. Asterisks indicate the significance of the difference between mean values obtained before and during exposure to ouabain in a given type of preparation (* = $P < 0.05$, ** = $P < 0.01$). NS = not significant.

rations values for MDP Amp and V_m at the distal site were similar to those recorded at the proximal site. Although values for APD₅₀ and APD₁₀₀ were respectively 9.2% and 12.5% less at the distal site than at the proximal site these differences were not significant. On the other hand in infarcted preparations the maximum diastolic potential and action potential amplitude were significantly reduced and APD₅₀ was significantly prolonged at the distal (infarcted) site when compared with the distal site in normal preparations. The prolongation of APD₅₀ was sufficiently great that action potentials recorded at the distal site in infarcted preparations were longer in duration than those recorded at the proximal site: the reverse of the situation observed in normal preparations. This prolongation was due primarily to a decrease in slope of phase 3 of the action potential since APD₁₀₀ while slightly prolonged was not significantly so.

In both types of preparation ouabain 2.5×10^{-6} M caused no change in MDP Amp, APD₅₀ and V_m at the distal site. In normal preparations the drug also did not affect APD₁₀₀ but in infarcted preparations it caused significant further prolongation of APD₁₀₀ by $6.8 \pm 2.0\%$ (mean \pm SEM, $p < 0.01$). Thus the discrepancy which existed under control conditions between the proximal and distal sites in the infarcted preparations with respect to APD₅₀ was increased by the addition of the drug.

Effects of ouabain on conduction and refractoriness (Table II) Under control conditions the conduction time of basic drive impulses from the proximal to the distal site was significantly

longer in infarcted than in normal preparations. Ouabain caused no change in normal preparations but in infarcted preparations the drug decreased conduction time by $22 \pm 9\%$ ($p < 0.05$) (Fig. 2).

Prior to superfusion with ouabain premature impulses introduced near the proximal site conducted rapidly to the distal site in normal preparations and there was little increase in conduction delay as the coupling interval between the basic drive and premature impulses was progressively decreased. This was presumably because action potential duration at the distal site was shorter than at the proximal site so that a premature impulse introduced at the proximal site would encounter progressively less refractory tissue as it propagated distally. For the same reason conduction block never occurred between the proximal and distal recording sites. Thus there was no significant difference in these preparations between the absolute refractory period of cells at the proximal site, the effective refractory period and the functional refractory period. Following superfusion with ouabain 2.5×10^{-6} M for 90 minutes there was modest prolongation of all refractory periods but this achieved statistical significance only for the functional refractory period.

In infarcted preparations unlike normal preparations premature impulses encountered progressively more refractory tissue as they propagated distally. Thus as the coupling interval between basic drive and premature impulses was decreased conduction time of the premature impulses from the proximal to the distal site

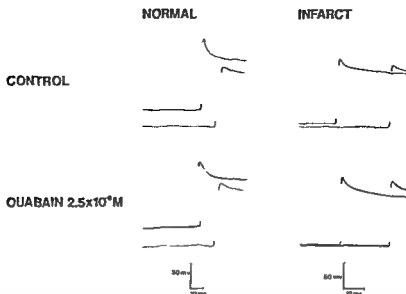


Fig 2 Effect of ouabain on conduction time between the proximal and distal recording sites in a normal preparation (*left panels*) and an infarcted preparation (*right panels*). The preparations were being driven at a cycle length of 800 msec. In each panel transmembrane potential recordings are displayed from two Purkinje fibres, one at the proximal and one at the distal site. In the normal preparation the resting membrane potentials of the two cells have been separated vertically while in the infarcted preparation they have been superimposed. In the normal preparation (*left panels*) conduction time between the two sites was 8.6 msec under control conditions. After exposure to ouabain 2.5×10^{-6} M for 90 minutes the conduction time was virtually unchanged at 8.7 msec. In the infarcted preparation (*right panels*) on the other hand conduction time was virtually unchanged at 8.7 msec during the control period to 20.0 msec after exposure to the same concentration of ouabain for the same period of time.

sites was also observed. The transmembrane potential readings were carefully examined for the presence of oscillatory afterpotentials following the last driven impulse and also for the presence of phase 4 depolarization during and after cessation of pacing.

In the experiments in which the effects of ouabain on refractoriness and conduction and on spontaneous activity were studied continuous impalements were not maintained throughout the experiments. When a microelectrode became dislodged from a cell it was replaced in another cell within the 1 mm² confines of the proximal or distal site.

Statistical analysis was carried out using Student's *t* test for comparing means of non independent samples to assess the significance of any change observed at a given site or in a given type of preparation (normal or infarcted). To compare data obtained from different sites or different types of preparation the *t* test for comparing means of independent samples was used. A *p* value of less than 0.05 was considered significant.

Results

1 Effects of Ouabain on Transmembrane Resting and Action Potential Characteristics

Proximal site (Table I) In both normal and infarcted preparations the proximal site was in a region of normal tissue. Under control conditions there was no difference between infarcted and normal tissue preparations with respect to maximum diastolic potential (MDP), action potential amplitude (Amp), action potential duration to 50% and 100% repolarization (APD₅₀ and APD₁₀₀ respectively) and maximum upstroke velocity of phase 0 (*V_m*) of the action potential of subendocardial Purkinje fibers at the proximal site. The addition of 2.5×10^{-6} M ouabain to the perfusate resulted in no significant change in any of these parameters.

Distal site (Table I) In infarcted preparations the distal site was in the infarcted region while in normal preparations it was in normal tissue. Prior to drug superfusion differences were observed at the distal site between the two types of preparation with respect to transmembrane resting and action potential characteristics. In normal prepa-

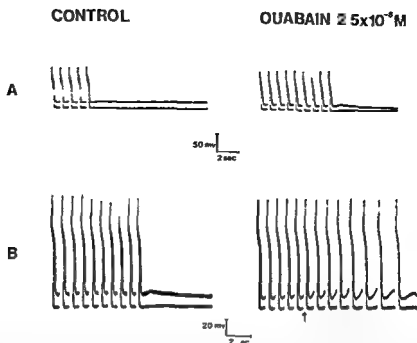


Fig 4 Ouabain induced oscillatory afterpotentials (OAP) A and B are from two different experiments conducted on infarcted tissue preparations. In each panel the upper trace is the transmembrane potential recording from a subendocardial Purkinje fiber at the distal (infarcted) site and the lower trace is from a fiber at the proximal (normal) site. In experiment A during control a stable resting membrane potential was attained and maintained at each site following cessation of pacing. After exposure to ouabain a stable resting membrane potential again followed the cessation of pacing at the proximal site but a single low amplitude OAP was observed at the distal site following the last driven action potential. In B there was a single low amplitude OAP at the distal site following the last driven response even during the control period. Following exposure to ouabain the last driven action potential (arrow) was followed by several OAP of large amplitude. These were initially of sufficient magnitude to bring the transmembrane potential to threshold resulting in action potentials which propagated from the distal to the proximal site. The amplitude and rate of depolarization of the OAP progressively decreased and the cycle length progressively increased until there was failure to reach threshold. Both during control and following ouabain the cell at the proximal site exhibited a stable resting membrane potential during phase 4.

site where the slope was about 25 mV/sec.

The eighth infarcted preparation exhibited a single oscillatory afterpotential at the distal site following cessation of pacing during the control period while at the proximal site a stable resting membrane potential occurred. Following exposure to ouabain variable spontaneous diastolic depolarization was evident only at the distal site during pacing and when pacing was interrupted several oscillatory afterpotentials of sufficient magnitude to reach threshold and initiate action potentials occurred at the distal site. These action potentials propagated to the proximal site where resting membrane potential remained stable during phase 4 (Fig 4B).

Discussion

The transmembrane resting and action potential characteristics of subendocardial Purkinje fibers and the functional properties of the suben-

docardial Purkinje fiber network which we observed under control conditions in both normal and infarcted preparations were generally similar to those which have been reported previously by other investigators.¹⁷⁻²¹ There were some minor differences however. In normal preparations we found that although the duration of action potentials at the distal site was shorter than at the proximal site the difference was not statistically significant. Others have found distal Purkinje fiber action potentials to be significantly shorter in duration than proximal action potentials.¹⁷⁻²¹ This discrepancy is probably due to the small number of experiments conducted on normal preparations in the present study since the mean values for APD₅₀ and APD₉₀ at both the proximal and distal sites were similar to those reported by others.¹⁷⁻²¹ In infarcted regions it has been previously reported that action potential duration is prolonged and resting membrane

increased and in two of six experiments there was conduction block between the two sites (Fig 3) In these preparations therefore the mean effective refractory period was longer than the absolute refractory period of the cells at the proximal site and the functional refractory period considerably exceeded the effective refractory period Ouabain caused prolongation of all three refractory periods the magnitude of which was statistically insignificant when compared with control values however (Fig 3)

3 Effects of ouabain on spontaneous activity

In five normal preparations the basic drive train of impulses was abruptly interrupted for 10 seconds during the control period In each case following the response to the last driven impulse the fibers at both the proximal and distal sites attained and maintained a stable resting membrane potential during the entire 10-second interruption and no undriven action potentials occurred An identical response was observed in every preparation when pacing was interrupted after 90 minutes of exposure to ouabain 2.5×10^{-6} M

The response to 10-second interruptions of basic drive impulses was also studied in eight infarcted preparations In seven of these preparations a stable resting membrane potential was maintained at both the proximal and distal sites following the last driven action potential and no spontaneous activity was observed during the interruption of pacing during the control period After exposure to ouabain the response was the same in two of these preparations In two additional experiments although a stable resting membrane potential occurred at both sites during the suspension of pacing several spontaneous action potentials occurred at progressively longer cycle lengths after the last driven response Each undriven response resulted in activation initially at the distal site followed after a brief interval by activation at the proximal site indicating that the impulses probably originated within the infarct In two more experiments following cessation of pacing after exposure to ouabain no spontaneous action potentials occurred but a single oscillatory afterpotential was observed at the distal site while at the proximal site a stable resting membrane potential followed the last driven response (Fig 4A) In the seventh preparation a stable spontaneous rhythm with a cycle length of 80 msec and with activation at the distal site preceding the proximal site occurred

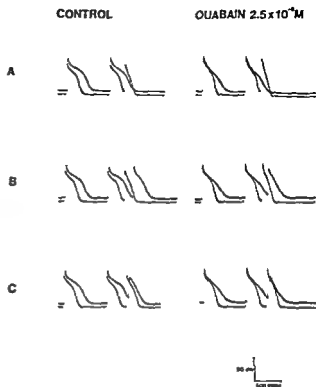


Fig 3 Effects of ouabain on the conduction of premature impulses in an infarcted tissue preparation In each panel the upper trace is recorded from a cell at the distal (infarcted) site and the lower trace is from a cell at the proximal (normal) site The left hand panels were recorded under control conditions while those on the right were obtained after exposure to ouabain 2.5×10^{-6} M for 90 minutes The first two action potentials in each panel are responses to basic drive stimuli at a cycle length of 800 msec and the third action potential is the response to a premature stimulus A shows the response to the earliest premature impulse which resulted in activation at the proximal site (absolute refractory period ARP) B shows the earliest premature response which conducted successfully to the distal site (effective refractory period ERP) and C shows the earliest obtainable premature response at the distal site to a premature impulse delivered near the proximal site (functional refractory period FRP) The ARP was 300 msec during control and 290 msec after ouabain The ERP was 320 msec under control conditions and 330 msec after ouabain These values differed from the ARP values because there was conduction block between the proximal and distal sites of the earliest premature responses both before and during exposure to ouabain (panel A) The FRP decreased from 400 msec during control to 390 msec after ouabain Both under control conditions and during exposure to ouabain the FRP considerably exceeded the ERP because there was marked conduction delay of early premature responses (compare panel B with panel C) The changes in ARP ERP and FRP after ouabain were not significant

after exposure to ouabain In this experiment stable phase 4 depolarization was evident at both sites after exposure to ouabain this was more marked at the distal site where the slope was approximately 5 mv/sec than at the proximal

velocity and failed to increase the functional refractory period in infarcted preparations unlike its effects in normal preparations. It might have been expected that the prolongation of action potential duration in infarcted regions induced by ouabain would have resulted in prolongation of the functional refractory period of infarcted preparations of even greater magnitude than occurred in normal preparations. The fact that this did not occur can be explained by the improvement in conduction which was observed. Why conduction improved is not certain. There are many possibilities including a change in the slope of the membrane responsiveness curve, a reduction of the threshold voltage, or alterations of the passive electrical properties of the Purkinje fibers making up the conduction pathway. It cannot be explained by the observed effects of ouabain on transmembrane resting and action potential characteristics in the regions studied but since these characteristics of Purkinje fibers surviving in infarcted regions are very non-uniform¹⁷ and since we only studied minimally depressed areas it is also possible that ouabain had effects on transmembrane resting and action potential characteristics of more depressed parts of the conduction pathway which would result in improved conduction such as an increase in amplitude or V_m . Finally, it is possible that phase 4 depolarization or oscillatory afterpotentials occurring in infarcted regions could facilitate conduction by bringing the transmembrane potential closer to the threshold potential.²⁰

In the present study there were also differences between normal and infarcted preparations with respect to the effects of ouabain on spontaneous activity. While there was no effect on any of the normal preparations, some form of spontaneous activity occurred in response to ouabain in six of the eight infarcted preparations studied. Stable phase 4 depolarization was observed in one preparation more marked in the infarcted region than in the normal one, and oscillatory afterpotentials were observed in the infarcted region in an additional three experiments. In the other two experiments spontaneous activity was manifested by the occurrence of several unstimulated beats at progressively increasing cycle lengths following the cessation of pacing, but the mechanism giving rise to these unstimulated responses was unclear since transmembrane potential was stable during phase 4 at both recording sites in these preparations.

Enhancement of phase 4 depolarization and the development of oscillatory afterpotentials are two well recognized mechanisms by which digitalis may induce spontaneous activity in Purkinje fibers.^{14, 15} The appearance of either of these phenomena has been reported to correlate well with the appearance of ventricular tachyarrhythmias in dogs given toxic doses of digitalis.¹⁶ The factors influencing the appearance of one or the other form of spontaneous activity are not well understood but Rosen and associates²¹ found that enhancement of phase 4 depolarization tended to appear more readily in damaged tissue or in the presence of a low concentration of potassium in the superfusing solution whereas oscillatory afterpotentials tended to occur in normal tissues superfused with solutions having a potassium concentration of 4 to 5.5 mM.²² Our observations are in agreement with theirs in that in the minimally depressed areas we studied within infarcted regions (average resting membrane potential = 78.6 mV) and with superfusion with modified Tyrode's solution having a potassium concentration of 4.0 mM, oscillatory afterpotentials were observed more commonly than enhanced phase 4 depolarization. It must be noted that whenever oscillatory afterpotentials were observed they occurred only in the infarcted region and that when phase 4 depolarization occurred it was more marked in the infarcted than in the normal region.

It is tempting to speculate on the possible clinical significance of our observations. In theory the effects of ouabain on spontaneous activity could be responsible for the appearance of toxic arrhythmias in an infarcted heart at a concentration of the drug which would be well tolerated by a normal heart. On the other hand, the observed improvement of conduction caused by ouabain in infarcted tissue preparations without a concomitant change in the functional refractory period would in theory tend to prevent or abolish arrhythmias due to reentrant mechanisms in infarcted hearts.³ We feel however that any attempt to extrapolate our results in this manner must be made with extreme caution. It requires the assumptions that subendocardial Purkinje fibers survive in regions of acute myocardial infarction in man as in dogs, that the surviving fibers have similar electrophysiological properties in the two species *in vitro* and *in vivo*, that the electrophysiological properties respond to digitalis in a similar manner, and that the concentration

potential action potential amplitude and V_m are variably depressed when compared with anatomically similar regions of noninfarcted hearts.¹⁷⁻¹⁹ Our observations are in agreement although because of a large standard deviation the depression of V_m was not statistically significant.

It should be noted that within the infarcted region we selected as the distal recording site an area in which resting membrane potential was not severely depressed and in which spontaneous diastolic depolarization was not evident when the preparation was being driven at a cycle length of 800 msec during the control period. This was done for two reasons. Firstly it has been reported previously that in 24 hour infarcted regions exhibiting severely depressed resting membrane potentials (i.e. less than -73 mv) do not maintain stable transmembrane resting or action potential characteristics over periods of several hours and hence would have been unsuitable for the present type of study.²¹ Secondly within the infarcted regions of different tissue preparations we wished to select areas with roughly similar baseline electrophysiological properties for study. We recognize that the areas studied were not representative of the entire infarcted region in that they were undoubtedly less depressed than the infarcted region as a whole.

It is well known that many hours of exposure to ouabain are required before a steady state is reached, and that inotropic effects occur long before any changes are demonstrable in transmembrane resting and action potential characteristics of normal mammalian ventricular myocardial cells and Purkinje fibers.² The initial electrophysiological effect in normal Purkinje fibers has been reported to be prolongation of the action potential² and to our knowledge this effect has not been observed in normal mammalian Purkinje fiber preparations exposed to a concentration of ouabain as low as 2.5×10^{-6} M for less than 5 hours when the preparations have been driven at cycle lengths of 800 msec or more—i.e. under the conditions of this study. Significant inotropic effects have been observed under these conditions however. Thus we believe the effects of ouabain observed in this study correspond to the effects of a therapeutic concentration of the glycoside. We recognize that the observations were made before a steady state was achieved and that more dramatic effects

would probably have been seen after longer exposure to the drug.

It is not surprising therefore that in the present study there was no effect of ouabain on transmembrane resting and action potential characteristics of subendocardial Purkinje fibers in normal preparations and in normal regions of infarcted preparations or on the conduction velocity and the effective refractory period in normal preparations. Despite this there was significant prolongation of the functional refractory period of normal preparations. The mechanism for this effect is not clear. The functional refractory period depends on both the refractory properties of the individual cells forming the conduction pathway and on the many other factors which determine the velocity and safety factor of conduction along the pathway such as membrane responsiveness threshold for excitation and the passive electrical properties of the conducting cells. We are not able to state which of these determinants were altered by ouabain or to what extent. It is apparent however that prolongation of the functional refractory period of normal Purkinje fibers is a more sensitive electrophysiological indicator of digitalis effect than is prolongation of the action potential duration a fact which has not been reported previously.

Within infarcted regions the effects of ouabain on surviving subendocardial Purkinje fibers differed from the effects on normal fibers in anatomically similar locations of normal noninfarcted hearts. As in normal preparations the drug caused no change in the resting membrane potential or in the amplitude and rate of rise of the action potential upstroke of the abnormal fibers in infarcted regions and no change in the effective refractory period of the infarcted preparations. It did however, cause significant prolongation of the action potential duration of fibers in infarcted regions. As previously noted prolongation of the action potential duration has been reported to be the earliest effect of digitalis on transmembrane resting and action potential characteristics of normal Purkinje fibers. The fact that ouabain under the conditions of this study caused prolongation of action potentials of Purkinje fibers in infarcted regions but not in normal regions indicates that the fibers in infarcted regions were more sensitive to this effect of the drug.

Ouabain also caused an increase in conduction

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of ouabain to which the tissues were exposed in our experiments corresponds to that to which tissues are exposed *in vivo* when a therapeutic dose of a cardiac glycoside is administered. In addition it is possible that other factors such as autonomic nervous system activity might modify the direct electrophysiological effects of digitalis *in vivo*. For example digitalis is known to exert a strong indirect effect on the normal heart by increasing vagal tone¹⁴ and enhanced vagal activity has been reported to inhibit ventricular arrhythmias in acute myocardial infarction. Acetyl choline the chemical mediator of vagal effects has been reported to abolish digitalis induced oscillatory afterpotentials in certain types of cardiac tissue.¹⁵ It is also important to note that the possible indirect effects of ouabain on the electrophysiological properties of cardiac tissues due to its effects on myocardial oxygen consumption have not been assessed in the present study. Finally since our results were obtained from tissue preparations made after infarction had been present for 24 hours they may have little relevance to arrhythmias occurring in the first few hours after myocardial infarction.² Thus while the present study has shown that the abnormal subendocardial Purkinje fibers surviving in regions of acute myocardial infarction in dogs have enhanced susceptibility to the direct electrophysiological effects of ouabain much further study is required before the clinical significance of this observation can be ascertained.

Summary

We compared the effects of ouabain 2.5×10^{-6} M on the electrophysiological properties of minimally depressed subendocardial Purkinje fibers surviving in regions of acute myocardial infarction with its effects on subendocardial Purkinje fibers in adjacent normal regions and in anatomically identical regions of noninfarcted hearts. Experiments were carried out *in vitro* on left ventricular tissue preparations dissected from the hearts of dogs 24 hours after coronary artery ligation and from normal canine hearts. Ouabain had no effect on maximum diastolic potential, action potential upstroke or V_m of Purkinje fibers in normal or infarcted regions. It prolonged the action potential duration in infarcted but not in normal regions. In infarcted tissue preparations ouabain increased conduction velocity and failed to alter the effective and functional refrac-

tory periods while in normal tissue preparations the drug did not affect conduction velocity or the effective refractory period but caused an increase in the functional refractory period. Ouabain did not cause spontaneous activity in normal tissue preparations. In infarcted preparations it resulted in spontaneous activity in six of eight preparations studied. This was due to the development of oscillatory afterpotentials in three preparations and phase 4 depolarization in one. In the other two preparations the mechanism was uncertain. Thus Purkinje fibers surviving in infarcted regions are more sensitive than normal fibers to the direct electrophysiological effects of digitalis.

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13. Compendium of Pharmaceuticals and Specialties

Table 1 Clinical and ECG findings at rest

| Athlete (initials & sport) | Age | Heart rate | ECG feature | T inversion leads | ST anomalies |
|-------------------------------|-----|---------------|----------------|----------------------|-----------------|
| 1 B V soccer | 20 | 60 | LVH RVH | ILL | - |
| 2 B P soccer | 20 | 44 | LVH | LPL, ILL | EPV |
| 3 C A soccer | 37 | 56 | - | LPL, ILL | - |
| 4 M M soccer | 20 | 45 | LVH RVH | RPL, ILL | - |
| 5 M A. canoeist | 17 | 54 | LVH | LPL | ERV |
| 6 M R. runner | 18 | 55 | - | ILL | - |
| 7 R G rugby | 18 | 70 | LVH | RPL, ILL | ERV |
| 8 S P basketball | 18 | 63 | LVH | LPL, ILL | - |

Abbreviations: LVH = left ventricular hypertrophy voltage criteria RVH = right ventricular hypertrophy voltage criteria RPL = right precordial leads LPL = left precordial leads ILL = inferior limb leads ERV = early repolarization variant.

mitral valve prolapse

spontaneous variability of T wave

infused intravenously in each subject to increase the heart rate (HR) at least 30 beats/minute. Infusion was adjusted to deliver 1 µg/ml. of IS within 30 seconds. Six athletes required a minimal dose of 5 µg to achieve the desired HR increase while two of them received 9 µg within 270 seconds. None experienced any ventricular premature beats during IS infusion. ECGs were recorded continuously up to third minute after the end of infusion and then at the fifth and tenth minute after infusion.

Twenty minutes after the end of IS infusion when the ECG had indicated the return to control tracings atropine sulfate (AT) was administered intravenously in a single dose of 0.02 mg/kg of body weight within 30 seconds. An AT test was performed in only seven of the eight subjects because one subject refused AT infusion. The ECG was monitored continuously up to the third minute after the end of infusion and then at the fifth, tenth, fifteenth and twentieth minute after infusion.

During pharmacological tests the VCG was recorded basally and when LCG tracings were made maximal effects of the drugs on the HR or T wave normalization were seen. ECG tracings were accurately analyzed for T wave polarity and amplitude and for QT and QTc intervals.²

Vectorcardiographic T loops in the frontal (FP) and horizontal planes (HP) were analyzed for (1) shape and sense of rotation (2) direction of maximum T vector ($\vec{V}_{max} T$) (3) QRS/T angle ($A^\circ QRS/T$) and (4) length/width ratio (L/W).

Results

Resting ECG and VCG patterns. Resting ECGs of all athletes are shown in Fig 1. ECG features

are also summarized in Table 1. Four subjects had moderate and two others had marked sinus bradycardia.

Four athletes fulfilled ECG voltage criteria of left ventricular hypertrophy (LVH) and two others had combined LVH and right ventricular hypertrophy (RVH). Isolated T wave abnormalities were appreciable in five cases and were associated with the early repolarization variant (ERV)¹⁶ in the remaining patients. Two subjects had T wave inversion in the inferior limb leads (ILL), one in the left precordial (LPL) and the remaining patient in both limb and precordial leads.

Case No 4 with MVP had a typical posterior inferior ischemia pattern¹⁷ together with a distinct terminal T wave inversion in the right precordial leads (RPL). Case Nos 2, 6 and 7 showed marked spontaneous variability of ECG tracings (see Fig 2). Resting QT and QTc intervals were within normal limits in all cases.

Resting VCG data are summarized in Table II.

QRS/T angle in the frontal plane was abnormally wide in Cases 1 and 3 and in the horizontal plane in Cases 2 and 3. T loop rotation in the horizontal plane was counterclockwise (CCW) and the inscription of the efferent limb of the loop was slower than that of the afferent limb in all cases. T loop shape in the horizontal plane showed a triangular pattern (see Figs 4 and 5) in four of six cases with negative T waves in the precordial leads and it was narrow in the remaining subjects. In the three subjects with ERV¹⁶ the ST vector oriented in the same direction as in the ECG tracings was appreciable. Vectorcardiogram confirmed the left ventricular

T wave abnormalities in top ranking athletes effects of isoproterenol atropine and physical exercise

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Many authors have reported ST and T wave abnormalities as an unexpected finding in the electrocardiograms (ECGs) of top ranking athletes otherwise asymptomatic and fit for excellent performance. Most of these authors agree about the benignity of these ECG anomalies especially when any evidence of organic heart disease is lacking.^{1, 2, 3, 39, 4}

Recently¹¹ however we reported 12 cases of asymptomatic top level athletes with pseudoischemic T wave changes, four of whom had asymptomatic mitral valve prolapse (MVP) and three who had an echocardiographic (ECHO) pattern of asymmetrical septal hypertrophy (ASH). Therefore the complete functionality of repolarization abnormalities in athletes is in our opinion at least questionable.

In the present work a further eight top ranking athletes with repolarization abnormalities were investigated in order to ascertain

1 if ECG anomalies could account for any concealed organic heart disease

2 the mechanism underlying these ECG abnormalities in athletes

3 the diagnostic reliability of provocative tests with regard to these repolarization disorders

Materials and methods

Clinical and ECG data are summarized in Table I. Eight top ranking athletes, males aged

between 17 and 37 years (mean 26 years) participating in different sports events, particularly in the endurance type, were referred to us by the Sports Medicine Institute of Rome (H Prof Venerando) for repolarization disorders. Seven subjects were examined during their competitive season when they were well trained. One subject (Case No. 3) was examined 10 months after he had finished his competitive activity while he was still maintaining his physical fitness. The follow-up of this athlete continued for 12 years. Another case (No. 5) had a follow-up period of 2 years. All the subjects were completely asymptomatic. Clinical examination and ECHO investigation were negative in seven of them. One athlete (Case No. 4) had auscultatory-echocardiographic features of mitral valve prolapse (MVP). ECG tracings at rest and after pharmacological tests were made with a Hewlett Packard (HP) multi-channel electrocardiograph. Orthogonal Leads X, Y, Z and VCG loops were recorded with a HP vectorcardiograph (Model 1507 A) using the Frank lead system.

Resting ECGs and VCGs were taken 10 minutes after the athlete had been kept in the recumbent position. ECG tracings were also recorded during and after rapid open hyperventilation (ROHV), Valsalva maneuver and standing.

Subsequently a stress exercise ECG (EX) was performed in all athletes first by a 3 minute step test (Harvard) and then by bicycle ergometer maximal effort test. On a second day after informed consent had been obtained a control ECG was recorded and thereafter a solution containing 1 µg/ml of isoproterenol (IS) was

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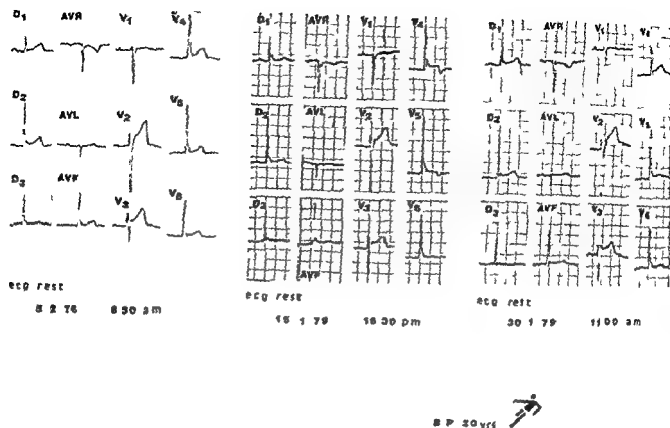


Fig 2 A 20 year old professional soccer player whose ECG tracings show marked spontaneous variability

Table II VCG findings at rest

| Case | QR loop | Frontal plane | | | | Horizontal plane | | | |
|------|---------|---------------|--------|---------------------------|-----|------------------|--------|---------------------------|-----|
| | | V max T | A QRST | T loop shape and rotation | L/W | V max T | A QRST | T loop shape and rotation | L/W |
| 1 | LVH | ~8 | 110 | narrow ∞ | ~ | 12 | 42 | wide CCW | 14 |
| 2 | LVH | 37 | 33 | narrow CCW | 3 | 65 | 120 | narrow CCW | 15 |
| 3 | — | 140 | 100 | wide CW | 14 | 175 | 207 | triangular CCW | — |
| 4 | LVH | 5 | 43 | narrow CCW | 3 | 330 | 45 | triangular CCW | — |
| 5 | — | 15 | 27 | wide CW | 0.8 | 55 | 41 | triangular CCW | — |
| 6 | — | 5 | 45 | narrow ∞ | — | 48 | 85 | wide CCW | 13 |
| 7 | — | 10 | 37 | narrow ∞ | 3 | 350 | 22 | triangular CCW | — |
| 8 | — | 10 | 15 | narrow CW | 5.6 | 37 | 79 | narrow CCW | 6 |

Abbreviations: L:H = length to height; A:QRST = QRS/T angle; Vmax T = maximum T vector direction; CW = clockwise; CCW = counter clockwise; $\alpha = 0^\circ$; β = 90° ; γ = 180° ; δ = 270° ; L:W = length/width ratio; mitral val = mitral valve; p-nalape = p-nalape

hypertrophy diagram is in Cases No 1 2 and 4

Provocative tests and exercise ECG. The ECG modifications induced by the Valsalva maneuver and ROHV were not the same in individual subjects (Table III). Standing worsened ECG abnormalities in six of eight cases (75%). Step test exercise normalized the ECG in six cases while maximal effort (Fig. 2) reverted the T wave in all subjects (100% of cases). All athletes achieved maximal HR and O₂ intake (VO₂ max) adequate

to their physical fitness. No subject exhibited pathologic ST changes or ventricular arrhythmias during and after effort.

Pharmacological tests Isoproterenol completely reverted the T wave (see examples in Figs 3, 4 and 5) in six cases (75%) and reduced T wave inversion in the remaining two. T wave modification was observed coincident with a combined increase of HR and a decrease of absolute QT interval. Average absolute QT interval at which T

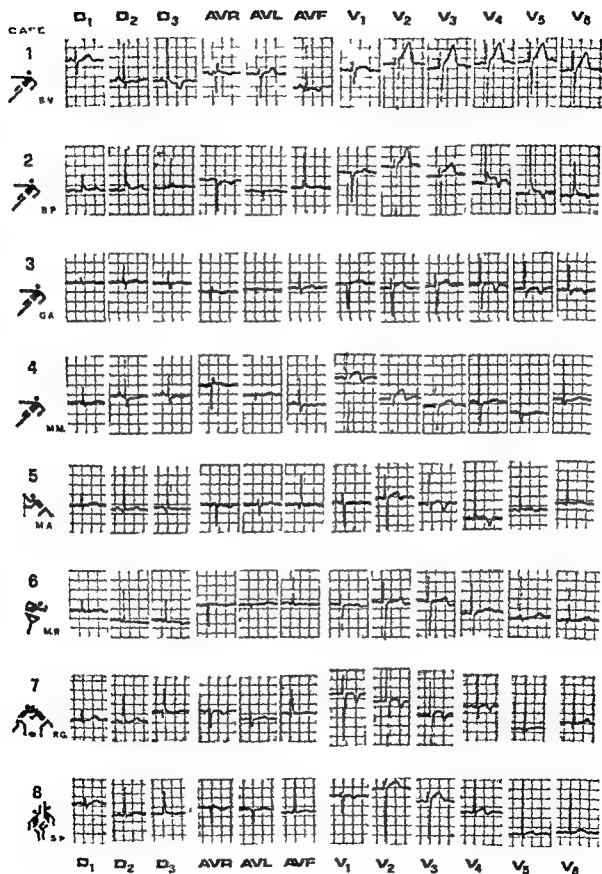
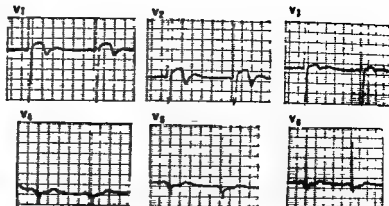


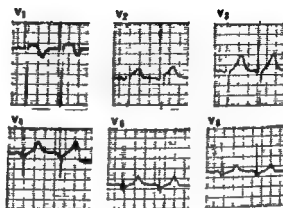
Fig 1 Resting ECG tracings

REST



ISOPREL 8 µg

AFTER 1



18 yrs



Fig 4 An 18-year-old professional soccer player with MVP. In this case also isoproterenol infusion reverted T wave abnormalities. H = VCG horizontal plane

even more intriguing because of its legal implications. Many authors observed spontaneous^{1,2,3,4} or provoked^{5,6,7} idiopathic T wave abnormalities in normal untrained persons with a higher percent incidence in Negroes (maximum 33.9%)^{8,9,10} than in Caucasians (average 0.5%)^{11,12,13,14}.

Epidemiological ECG screening performed in an unselected white population of 12,000 sports men participating in different physical activities and belonging to various competitive levels evidenced a percent incidence of T wave abnormalities (0.5%) similar to that of untrained people. With regard to selected highly trained groups the percent incidence of major repolarization disorders ranges between 4.1 and 18%^{15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}. This supports the opinion that T wave abnormalities are more frequent in top level athletes especially when they practice an endurance activity. This observation suggested the hypothesis that intensive

training could play a role in the pathogenesis of such repolarization disorders.

T wave abnormalities may be produced by central nervous system disease.² In addition T wave and QT interval modifications have been experimentally induced either by unilateral stimulation or by removal of stellate ganglia^{22,23} or by brief or prolonged cardiac nerve stimulation or catecholamine infusion. Moreover changes in T wave amplitude or polarity were obtained in dogs by isoproterenol infusion into different regions of ventricular myocardium.²⁴ Daoud and co-workers²⁵ emphasized that isoproterenol reverts more than 90% of primary T wave abnormalities not due to pericarditis or ischemia while it does not normalize secondary T wave changes.

Neither atropine infusion nor atrial pacing were effective in normalizing T wave polarity. T wave normalization after isoproterenol therefore should not be related only to HR increase but to a combination of a critical increase of HR and

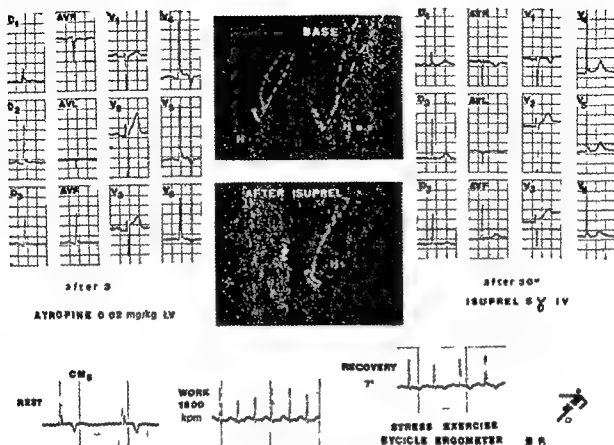


Fig 3 The same patient as shown in Fig 1. Note complete normalization of T wave abnormalities after isoproterenol infusion and exercise. H = VCG horizontal plane.

Table III Effects of provocative tests: exercise, isoproterenol and atropine upon T wave abnormalities

| Case | At rest | Hyperventilation | Standing | Exercise | Isoproterenol | Atropine |
|------|------------|------------------|-----------|------------|---------------|-----------|
| 1 | unchanged | unchanged | unchanged | normalized | normalized | unchanged |
| 2 | unchanged | reduced | worsened | normalized | normalized | unchanged |
| 3 | reduced | reduced | worsened | normalized | reduced | — |
| 4 | unchanged | reduced | worsened | normalized | normalized | unchanged |
| 5 | worsened | worsened | worsened | normalized | normalized | reduced |
| 6 | worsened | unchanged | unchanged | normalized | normalized | unchanged |
| 7 | normalized | worsened | worsened | normalized | reduced | worsened |
| 8 | reduced | reduced | worsened | normalized | normalized | unchanged |

wave normalization had been observed was 0.34 ± 0.04 sec with an average HR of 90.1 ± 14.1 beats/minute.

Despite a greater increase of HR (average 105.8 ± 8.82 beats/minute) and a similar QT interval shortening (average 0.34 ± 0.03 beats/minute) AT infusion did not significantly change T wave amplitude or polarity in five cases, reduced T wave inversion in 1 case and worsened it in another case.

Discussion

ST and T wave abnormalities simulating pericarditis or myocardial ischemia in asymptomatic subjects without clinical or instrumental evidence of cardiopathies have long since represented a cardiological puzzle. Moreover when these anomalies are encountered in athletes otherwise suited for excellent cardiovascular performance and who participate in intensive training and exhaustive competitions, the problem is

particularly in females^{15 19 21 22} mostly with benign prognosis^{1 2 9 10 17 23 24} even if cases of sudden death and myocardial infarction were reported. Since MVP had been discovered also in asymptomatic excellent athletes^{25 26} a new problem arose about the significance of this finding. Therefore this study was conducted to assess the advisability of allowing physical activity in these subjects.

A more detailed discussion on this argument is beyond the limits of this work, but we think in agreement with Barlow's opinion²⁷ that an asymptomatic athlete with MVP should be allowed to take part in his sport activity, provided that he did not experience ventricular tachyarrhythmias during effort.

Notwithstanding this great volume of studies the pathogenesis and significance of ischemic ECG changes in MVP still remain substantially obscure. In our previous experience¹ T wave abnormalities in top ranking athletes with an ECHO pattern of MVP had their abnormalities reverted by maximal effort in three out of four cases. This behavior was also observed in a further four subjects (unpublished data).

An isoproterenol test has been performed only in the athlete with MVP included in this study (Fig. 4) who achieved a complete normalization of the T wave pattern. Although a large number of cases should be investigated to ascertain the reliability of the isoproterenol test in athletes with MVP and an ECG ischemic pattern we suggest that the presence of repolarization disorders in asymptomatic and arrhythmia free athletes with MVP must be considered with caution and requires a more detailed investigation only when exercise and isoproterenol test do not revert these abnormalities.

Summary

Eight cases of top ranking athletes with "repolarization disorders" are reported. All subjects were asymptomatic and were otherwise suited for excellent cardiovascular performances. Seven athletes did not show any evidence of heart disease. Seven had MVP (mitral valve prolapse).

Unprompted variability of ECG tracings was observed in three cases. Both isoproterenol infusion (IS) and maximal physical effort (EX) normalized T wave abnormalities in 100% of cases while atropine A.D. was ineffective despite

an increase in heart rate greater than that caused by IS. The authors emphasize the usefulness of a combined use of the EX and IS tests in ascertaining the clinical significance of T wave changes in healthy athletes.

A neurogenic mechanism is proposed by the authors for the pathogenesis of these T wave abnormalities. This hypothesis may explain the unprompted variability of ECG tracings and T wave normalization after maximal physical effort and isoproterenol infusion.

We thank Professor A. Venerando of the Sports Medicine Institute of Rome for his continuing encouragement and support of our studies and for his assistance in the functional evaluation of the athletes included in this study. We are also grateful to Mr. Madeddu Alessandro for his assistance in preparing the tables, figures, and the manuscript.

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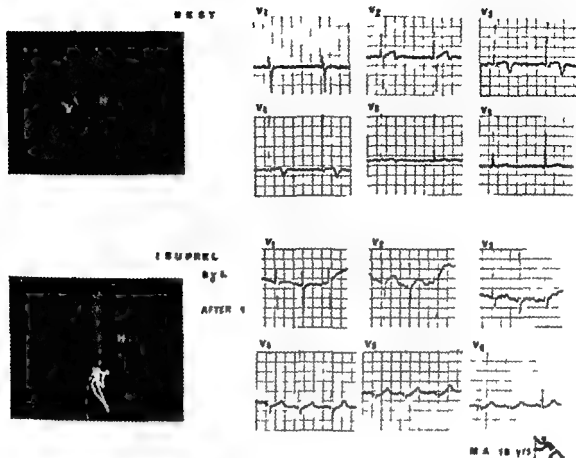


Fig 5 An 18-year-old canoeist (olympic rankin). The complete normalization of the T wave pattern after isoproterenol infusion is clearly appreciable both on the ECG and on the VCG. $H = VCG$ horizontal plane

decrease of absolute QT interval duration caused by this drug. Isoproterenol shortens monophasic action potential (MAP) duration due to the shortening of phase 2.²¹ This could explain the different effects of isoproterenol on normal and abnormal primary T wave changes. In this regard we suggest that T wave abnormalities in top ranking athletes without clinical signs of organic heart disease if reverted by isoproterenol infusion or maximal physical effort should be considered functional. We are in favor that such a diagnostic approach be routinely employed in these cases even if further investigation in a larger number of cases is required to define better the sensitivity and specificity of these tests.

Pathogenesis of T wave abnormalities. We have already suggested that primary T wave abnormalities in athletes could be neurogenic. Prolonged physical training in fact is probably associated with both a decrease of resting vagal and sympathetic tone. This could unmask in

genetically predisposed athletes a latent functional asymmetry of cardiac sympathetic nerves and induce inequality of ventricular repolarization resulting in T wave abnormalities.¹ The normalization of ventricular repolarization obtained by both isoproterenol infusion and maximal effort could be explained as due to a uniform enhancement of sympathetic tone at high levels which overcomes functional asymmetry of resting cardiac sympathetic discharge.

T wave abnormalities in MVP. T wave abnormalities in subjects with MVP are a relatively common finding either as a typical posterior-lateral "inferior ischemia" pattern or less frequently as diffuse T wave inversion.^{22-24, 25} In addition patients with MVP have other ECG anomalies like atrioventricular conduction disturbances² and supraventricular and ventricular arrhythmias at rest and during effort.^{22, 23, 26-28} Nevertheless MVP is a tremendously common finding in normal subjects

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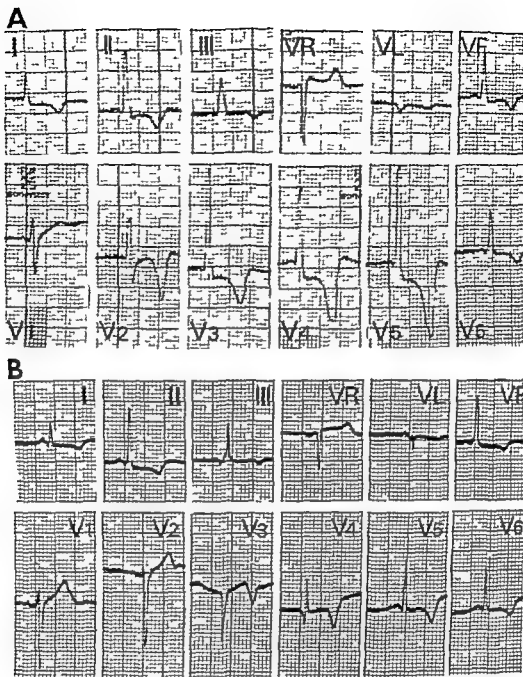


Fig 1 Pre (A) and postoperative (B) electrocardiograms. Both tracings show a short PR interval (0.11 sec). New q waves (Leads V₁ and V₂) are present after surgery.

left ventricular aneurysm was not different from that obtained preoperatively and selective coronary arteriography (Fig 3) revealed complete release of the systolic obstruction of the LAD.

Discussion

As far back as 1922 Craicianu described for the first time the intramural course of a segment of the left anterior descending coronary artery. The frequency of this anomaly is relatively

high as pointed out by Geuninger¹ who found an incidence rate of 23% in his autopsy series. Intramural segment occlusion is by far less common and it has been documented in about 0.5% of patients undergoing coronary arteriography.

The ischemic nature of chest pain associated with significant systolic constriction of the LAD has been demonstrated in a group of subjects with milking effect and otherwise normal coronary arteries. These patients showed myocardial lac-

Case reports

Relief of angina by periarterial muscle resection of myocardial bridges

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Systolic segmental narrowing of the left anterior descending coronary artery has been related to the presence of myocardial bridges.¹ Transient arterial constriction by muscle entrapment produces a characteristic milking effect which is easily recognized on angiography.² Patients with significant obstruction of the squeezed artery may develop ischemic chest pain. It has been suggested that periarterial muscle resection to decompress the embedded vessel could be beneficial in selected cases.³ Only five patients with this uncommon anomaly have been previously operated upon using such a technique,⁴ but late follow up studies are lacking. Two other cases have recently been reported in which arterial debridging was associated with revascularization procedures.⁵

This report documents a case of milking effect studied both before and 11 months after surgical repair of two myocardial bridges causing transient (systolic) occlusion of the left anterior descending coronary artery.

Case report

A 44-year-old man was admitted to the Hospital Clinico University of Barcelona in May 1976 for investigation of chest pain starting one year prior to admission. Pain was related to exertion and was relieved by nitroglycerin. The patient was severely incapacitated (Class III NYHA) in spite

of medical treatment with sedative, long acting nitrates and beta blocking agents. Past history included typhoid fever (1941) and two operations: a gastrectomy (1943) and a cholecystectomy (1950). Cardiovascular examination revealed a soft S heart sound at the apex with no murmurs. The heart rate was 60 beats per minute. Blood pressure was 110/70 mm Hg. Peripheral pulses were all palpable. There were no signs of heart failure. Chest x ray showed a normal sized heart. The ECG (Fig 1) revealed sinus rhythm, a short PR interval (0.11 sec) with notched QRS upstroke and no definite delta waves. Tall R waves (Leads V₁ to V₄) and ST segment depression with deep inverted T waves in all leads. Routine laboratory data were normal. Transverse LV dimensions as well as wall motion and wall thickness were judged normal by echocardiography. An exercise test was discontinued because of chest pain and ST changes. Double product at peak exercise was 1700 mm Hg/minute (heart rate 110 beats per minute and systolic blood pressure was 160 mm Hg).

Combined right and retrograde left heart catheterization was carried out by the percutaneous technique. No valvular or subvalvular pressure gradient was demonstrated. Left ventricular end-diastolic pressure was moderately increased (94 mm Hg). Cardiac index was normal (3 L/min/M²). A left ventricular angiogram showed normal volumes and mass with an ejection fraction of 40%. There was no mitral regurgitation. Selective coronary angiography (Fig 2) demonstrated complete systolic occlusion on two different segments of the LAD at its mid third. The distal vessel was relatively narrow and short as it did not reach the apex. The dominant in-bifurcated coronary artery, as well as the circumflex were entirely normal.

Periarterial muscle resection was performed in June 1976. The mid third of the LAD was found to course close to the endocardium and its liberation resulted in right ventricular perforation. The defect was repaired and the postoperative course was uneventful despite the appearance of new q waves in Leads V₁ and V₂ (Fig 1). Since surgery the patient has remained asymptomatic of his chest pain. A maximal exercise test performed in January 1977 was negative (double product 2100 mm Hg/minute). A second hemodynamic study done 11 months after muscle resection showed normal LVEDP (10 mm Hg) and borderline cardiac index (2.5 L/min/M²). The

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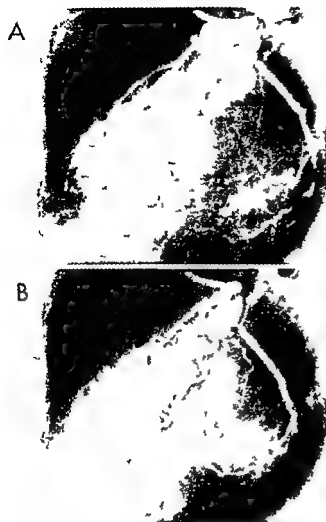


Fig 3 Diastolic (A) and systolic (B) frames showing release of obstruction following periarterial muscle resection

terial bridging and aortocoronary bypass grafting are probably not required in most patients with mural coronaries when arterial entrapment is not associated with fixed obstructions. The lack of success of unnecessary combined procedures may be due to hemodynamic burden derived from flow competition.

Summary

A 47 year old man presented with exertional angina. Selective coronary arteriography showed complete systolic segmental occlusion of the left anterior descending coronary artery producing

milking effect. Permanent relief of symptoms was achieved by surgical excision of myocardial bridges. Postoperative angiography performed 11 months later was normal. Periarterial muscle resection should be considered in symptomatic patients with this rare anomaly.

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tate production and ST segment depression on the ECG during atrial pacing. Thus ischemia seems to be triggered by a critical shortening of the diastolic filling period that compromises local O₂ delivery.

The intramural location of the LAD in the embryo points toward a congenital origin of this anomaly. Although the delayed appearance of symptoms remains unclear, it has been postulated that the acquisition of the milking effect could be secondary to progressive muscle growth and hypertrophy.⁹ Four out of 11 patients studied by Noble and associates had left ventricular hypertrophy and one of them was found to have a mild muscular subaortic stenosis. Septal perforator compression has recently been documented in subjects with idiopathic hypertrophic subaortic stenosis.¹⁰ Slany and co-workers reported a case in which histologic examination of excised muscle showed a marked thickening of fibers. The finding of tall R waves in our case is in keeping with the diagnosis of hypertrophy, but analysis of the angiograms revealed a normal left ventricular mass. In addition, echocardiographic assessment of both septal and posterior wall thickness was also normal. Interestingly enough, the LVEDP became normal after surgery and its dramatic reduction suggests, in spite of a moderate fall in stroke volume, an improvement in left ventricular compliance. Reversal of ischemia suggested by decreased ST segment depression after surgery provides a satisfactory explanation for this finding.

The presence of new q waves deserves comments. Their appearance following revascularization procedures has been related to the occurrence of a myocardial infarction at the time of surgery, an hypothesis substantiated by the finding of LV wall motion abnormalities in corresponding segments.¹¹ Since the second angiogram was unchanged, infarction is unlikely. Absence of infarction is also suggested by the regression of a previously elevated LVEDP. On the other hand, the LAD was not opened or hurt during the operation and it was found to be patent afterwards. A logical explanation for the appearance of new precordial q waves is provided by the development of a septal focal block, this form of segmental conduction disturbance being a consequence of the full thickness myotomy. Pre-excitation does not seem to account for the presence of new q waves as they were confined to Leads V₁

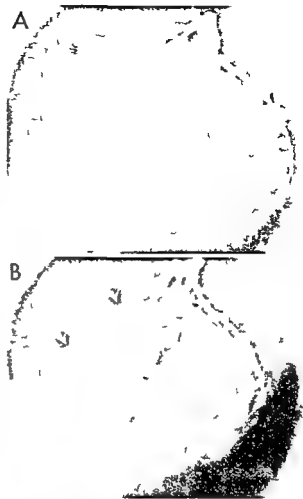


Fig. 2. Preoperative left coronary angiograms (lateral view) in diastole (A) and systole (B). Note that the LAD becomes occluded (arrows) in systole.

and V while the remaining leads did not show AV conduction changes. In addition, ajmaline administration failed to modify the atrioventricular conduction pattern.

Prognosis of this anomaly is unknown. Unexpected sudden death attributed to myocardial bridges has never been confirmed. Disagreement exists in regard to their relationship with coronary atherosclerosis.¹² If one accepts that they play a role in the genesis of atheroma, excision of bridges would undoubtedly be beneficial. Release of obstruction may result in permanent relief of symptoms as demonstrated in our patient who remains free of angina 27 months after surgery. Therefore, it seems reasonable to recommend corrective surgery in disabled patients with significant systolic arterial constriction due to myocardial bridges. Combined periar-



Fig 1 High power magnification of an area of skeletal muscle showing infiltration by eosinophilic granular cells with areas of focal necrosis and nuclear anaplasia

Shortly after admission right ventricular pacemaking was established but the pacer failed to capture at times due to perforation into the pericardial cavity. A permanent epicardial pacemaker was placed via a left anterior thoracotomy. At thoracotomy numerous greyish nodules were found throughout the myocardium, the pericardium, the lungs, and the pleura. Four hundred milliliters of bloody pericardial fluid were drained.

Biopsies of the myocardium, pericardium, lung, and pleura were obtained. Histological examination of the myocardial specimen revealed complete replacement of the myocardial tissue by granular cell tumor, histologically similar to that obtained from the previous axillary and subcutaneous shoulder lesion. Again, no increase in mitotic activity was noted. There was some nuclear anisocytosis but no anaplasia or necrosis. The lung specimen showed a subpleural nodule extending into the pulmonary parenchyma composed of well differentiated granular cells.

The patient was discharged from hospital 14 days later with good pacemaker function and was maintained on digitalis and diuretics until her death four months after discharge. Autopsy permission was refused.

Discussion

GCM is considered to be a rare tumor of soft tissue. Nevertheless, many cases were reported

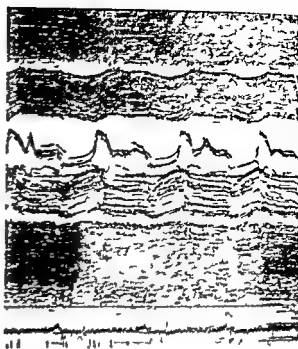


Fig 2 The echocardiogram shows marked thickening of the interventricular septum and the posterior left ventricular wall with diminution in the diameter of the left ventricular cavity. There is a small posterior pericardial effusion.

since 1926 when Abrikossoff described in detail the features of the tumor. The term myoblastoma was questioned by some, and many other terms have been proposed. No agreement exists regarding the tumor's biological nature and origins. Derivation from precursors of voluntary muscle cells, viral factors, response to parasitic infection, perineural degeneration, metabolic alterations, lipid thesaurismosis, degeneration of the muscle fibers, and derivation from Schwann cells have been suggested.

GCM is most frequently found in oropharyngeal and subcutaneous tissue, but its occurrence in a wide variety of sites has been well documented.¹ It may occur in the eyelid, breast, colon, ovaries, or bronchus.

It is believed that the tumor is generally nonmalignant and rarely metastasizing,^{2,11} although accounts of malignant forms have been reported.^{13,16} The tumor appears to be more frequent in women and blacks, with a higher incidence in the third and fourth decades.¹

Strong and colleagues et al¹¹ reported three malignant lesions in their series of 95 cases, one of which was cured by reexcision. Their statement that tumor size, rapidity of growth, and invasion of adjacent structures may be more significant features in differentiation of benign from malignant

Malignant granular cell myoblastoma with metastatic cardiac involvement Case report and echocardiogram

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Granular cell myoblastoma (GCM) is a rare soft tissue tumor of which the vast majority are benign. Our case concerns a malignant variety which presented clinically as heart block.

The echocardiographic findings are described together with the histological findings in the primary tumor and the metastatically infiltrated myocardium.

Case report

The patient was a Caucasian female who was 43 years old at the time of the final admission.

Two years previously she had had a mass excised from the left deltoid muscle. The pathological specimen was a 7 by 5 by 4.2 cm mass consisting of firm grey brown tissue with admixed gritty white areas. The tumor was composed histologically of regular cuboidal cells with granular eosinophilic cytoplasm and small central nuclei. Most of the specimen was organized into small packages separated by connective tissue septae but in one area there was focal necrosis with the adjacent cells showing some anaplasia. Included in this zone were a few atypical mitotic forms. In view of the paucity of mitotic activity the diagnosis of a benign granular cell myoblastoma was made.

Approximately one year later the mass recurred with axillary lymphadenopathy. Repeat biopsy (Fig 1) was performed. The specimen showed infiltration of the muscle by large masses of eosinophilic granular cells with focal areas of nuclear anaplasia and giantism. In view of the course of the disease the diagnosis was changed to malignant granular cell

myoblastoma in spite of the persistent relative paucity of mitotic activity and cellular pleomorphism. Further investigations in search of metastatic disease were carried out including mammography, lung scan, liver and spleen scan and bone marrow biopsy which were all normal.

Radiographs of the lumbar vertebrae showed sclerotic changes and the isotope bone scan showed widespread metastases in the pelvic ribs and spine.

On the final admission the patient was pale and thin on examination. Blood pressure was 90/50. The heart rate was 20/minute. Jugular venous pressure was 12 cm H₂O and a left ventricular gallop was heard. The liver was smooth, soft and slightly enlarged. No evidence of lymphatic enlargement was found.

The chest x-ray showed cardiomegaly with pulmonary hilar congestion. The CBC was normal. SGOT, LDH and alkaline phosphatase were moderately elevated. The protein and immunoelectrophoresis were normal. ECG showed a 1° block of third degree with effective heart rate of 98 per minute and an atrial rate of 80 per minute. Later while monitoring the patient long episodes of asystole (the longest 6 seconds) were demonstrated. Occasionally the patient was in sinus rhythm with a right bundle branch block and left anterior hemiblock. Complete left bundle branch block was transiently present on the ECG.

Echocardiography (Fig 2). Standard M mode echocardiography was performed using commercially available equipment. Recordings were made with a 3.5 MHz transducer and recorded with a Honeywell strip chart recorder CRT Visucorder 1838.

The echocardiogram showed marked symmetrical thickening of the interventricular septum (22 mm) and the posterior wall of the left ventricle (20 mm). No systolic change in thickness of the interventricular septum and only 2 mm further thickening of the posterior left ventricular wall occurred.

The left ventricular cavity was reduced on size with diastolic and systolic diameters of 34 mm and 30 mm, respectively. There was dilatation of the left atrium (15 mm). The EF slope of the anterior leaflet of the mitral valve was decreased (62 mm/sec). A small posterior pericardial effusion was present. Based on these findings a diagnosis of infiltrative cardiomyopathy was made.

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Infarct expansion The 'second event' after acute myocardial infarction

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Clinical course

This 57 year old male was in excellent health until one day prior to admission when he first noted substernal chest pain, like indigestion. He presented to the emergency room after the pain persisted for two hours. An electrocardiogram was normal (Fig 1) and he was sent home. Thirty six hours later he returned to the emergency room because of unremitting chest pain of increasing severity. The electrocardiogram demonstrated changes of an acute anterior myocardial infarction (Fig 2) and he was admitted.

The patient's medical history was remarkable for excellent health. He had no previous cardiorespiratory symptoms and took no medications. His cardiac risk factors included a 70 pack year smoking history and a positive family history with a brother succumbing to a myocardial infarction at age 55.

The blood pressure was 90/60 mm Hg, pulse rate 70 per minute and regular, respiratory rate 14 per minute. There was no jugular venous distention. Basilar rales were audible in both lung fields. The precordium was quiet with no palpable heaves. The point of maximal impulse was in the fifth left intercostal space in the mid clavicular line. The first and second heart sounds were normal. No murmurs were heard but an S gallop was present. No hepatosplenomegaly or peripheral edema was present. The admission chest radiograph revealed bilateral interstitial infiltrates and

minimal cardiomegaly. The admission electrocardiogram demonstrated changes of an acute anterior myocardial infarction with prominent ST segment elevation in Leads I, aV_L and V through V₅ and ST segment depression in the inferior leads. New Q waves were present in Leads V₁ and V₂ that were not present in the previous day's electrocardiogram.

The chest pain was relieved with 3 mg of intravenous morphine sulfate. After an initial diuresis with a total of 60 mg of intravenous furosemide he did well with no dyspnea, no further chest pain, no arrhythmias, good urine output and a stable blood pressure of 110/70 mm Hg. The peak CK value was 850 IU/L. This was obtained on admission with declining serial values over the first 24 hours of admission. The electrocardiogram evolved Q waves in Leads V₁ through V₅, persistent to 2 to 3 mm ST segment elevation in Leads V through V₅, and lesser elevation in Leads I, aV_L and V. There was minimal ST depression in the inferior leads. He did well until six days after admission when he complained of chest pain and shortness of breath. Physical examination revealed a blood pressure of 85/60 mm Hg and rales to the infrascapular border bilaterally. No rubs and no new murmurs were audible. An S gallop was present but no abnormal precordial pulsations were noted. The chest radiograph demonstrated a prominent bilateral perihilar alveolar and interstitial infiltrate and minimal increase in the cardiac silhouette from admission. The electrocardiogram demonstrated the evolution of an anterior myocardial infarction as well as acute ischemic changes with further ST segment elevation in Leads I, aV_L and V through V and further depression in the inferior leads than was present on tracings taken since admission (Fig 3). Serial CK values obtained at 4 hour intervals over the

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nant types would seem to be borne out by our case

Moscovic and Azar¹⁸ observed that in one third of the cases the onset of a second or multiple tumors was preceded by surgical or therapeutic manipulation of the primary lesion

Radiation therapy was generally disappointing¹¹ but Hunter and Dewar⁷ give it some merit and describe survival times two or three times longer in treated than in untreated patients

To our knowledge the role of chemotherapy has not yet been established

Primary cardiac involvement by GCM was reported by Roth and Spain in 1952 in a patient with congestive cardiac failure The tumor involved pericardial and myocardial tissues at the left atrial level above the atrioventricular sulcus

Disseminating metastasizing GCM with multi-system involvement including pericardium and myocardium was reported by Svejda and Horn¹⁶ and by Khanolkar¹⁷ Our case is to our knowledge the third reported case of metastasizing GCM with cardiac involvement Our patient was a middle aged woman who twice had surgical intervention and had a primary muscular tumor A one year history of mild shortness of breath did not alarm her and it was the syncope attack that brought her to a cardiologist's attention Complete A V block and episodes of asystole were the most dramatic events The echocardiogram with thickened ventricular walls and reduced interventricular septal and posterior left ventricular wall motion showed changes characteristic of infiltrative myopathy Associated were increased left atrial diameter and the presence of a pericardial effusion The causes of symmetrical septal hypertrophy such as left ventricular pressure overload were not present The patient's history together with the radiographic and isotope findings in the spine suggested metastatic disease The echogenic features could not be distinguished from the other causes of infiltrative cardiomyopathy

Morbid anatomical features strongly resemble the case of Khanolkar¹⁷ with the myocardium being sprinkled with numerous tumor nodules

Despite the extensive involvement by tumor the patient managed to survive the acute situation with A V block and she lived with a pacemaker for four months after her discharge from the hospital

Summary

A malignant form of granular cell myoblastoma originating in the shoulder gave rise to metastatic cardiac involvement causing infiltrative cardiomyopathy with heart block The patient survived four months with a permanent pacemaker The echocardiographic and histological features are described and the literature is reviewed Features shown on the echocardiogram are indistinguishable from other causes of infiltrative cardiomyopathies

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next 24 hours remained within normal limits. He was treated with intravenous morphine sulfate and furosemide with resolution of his symptoms and return of the ST segments to their position prior to this episode with persistent precordial elevation. The next day he had another episode of chest pain and shortness of breath. There were no associated ECG changes or CK elevation. The chest pain was quickly relieved with morphine sulfate but despite furosemide and digoxin he continued to have slight shortness of breath and evidence of persistent pulmonary congestion on physical examination and chest radiograph. After another episode of chest discomfort he was placed on nitroglycerin ointment which was well tolerated. He had no further chest discomfort. However 21 days after admission he unexpectedly developed ventricular tachycardia. Despite repeated attempts at electrical cardioversion and extensive resuscitation efforts he was unable to maintain a pulse or blood pressure.

Clinical discussion

DR KENNETH J SILVERMAN This case raises the common problem of a patient with a stable presentation and initially uneventful course following an acute myocardial infarction who rapidly and unexpectedly deteriorates with further chest pain or heart failure. To maximize the patient's chance of survival the etiology of the patient's deterioration must be established quickly with a minimum of risk. Extension of the myocardial infarction, ventricular septal rupture, ventricular free wall rupture, papillary muscle rupture or dysfunction, ventricular aneurysm formation, pericarditis and pulmonary embolism are complications that must be carefully considered.

Recurrence of chest pain, onset of heart failure, re-elevation of ST segments and re-elevation of CK are clues to myocardial infarct extension. A study utilizing serial precordial ST segment mapping and serial CK values demonstrated evidence of infarct extension in greater than 50% of acute transmural anterior myocardial infarctions at an average of 5.8 days after admission. The extension of myocardial injury may seriously compromise cardiac function and is a major determinant of mortality.

Ventricular septal rupture complicates from 1% to 2% of all myocardial infarctions. The infarct is usually transmural and the rupture usually

occurs within the first week. The presentation is often an abrupt deterioration in clinical status, with left ventricular failure, a new pansystolic thrill and a loud pansystolic murmur. There may be further chest pain at this time. Although the prognosis is poor, death is often not sudden, permitting time for diagnosis and treatment.

Rupture of the free wall of the ventricle is a rare but catastrophic event with an average incidence of approximately 7% in autopsy series of patients with acute myocardial infarctions. Rupture is more common in patients suffering their first transmural infarction and may involve the anterior wall more frequently. The most common presentation is sudden death usually within the first week after infarction. There are no characteristic features of the examination after rupture although findings consistent with cardiac tamponade may be present if there is slow leakage of blood and a blood pressure was maintained. Sudden increase in amplitude of the T wave or reversal of previously inverted T waves has been described as a clue to the possibility of acute hemopericardium. Some patients may experience repeated and prolonged chest pain which may be an indication of impending rupture with slow leakage of blood into the pericardium.^{1,2}

Papillary muscle rupture has been noted at autopsy in as many as 5% of acute myocardial infarctions.³ It is not related to the size of the infarction, most frequently occurring in infarctions that are relatively small in size and posterior in location. The presentation is similar to ventricular septal rupture with dramatic deterioration in the patient's condition most frequently within the first week, occasionally associated with chest pain. There is evidence of left ventricular failure and usually a loud pansystolic murmur but a prominent thrill is unusual. Like ventricular septal rupture, death is not sudden, permitting time for diagnosis and treatment.

Differentiating between ventricular septal rupture and papillary muscle rupture in a patient with sudden deterioration and a new systolic murmur can be difficult and may require insertion of a flow directed balloon catheter. An increase in the oxygen saturation on passing from the right atrium to the right ventricle is evidence of a ventricular septal defect while prominent regurgitant V waves on the pulmonary capillary wedge tracing is evidence of mitral regurgitation.

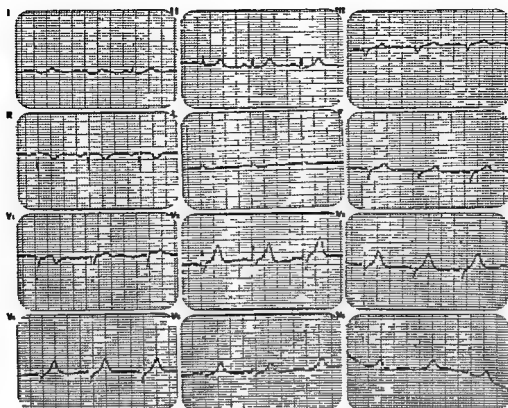


Fig 1 Initial 12 lead electrocardiogram within limits with no acute ischemic changes

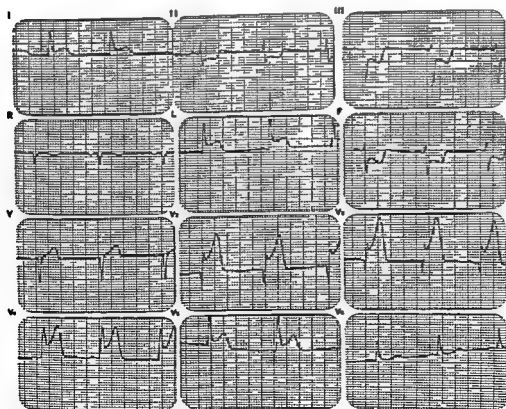


Fig 2 ECG taken on admission reveal changes of an acute anterior myocardial infarction

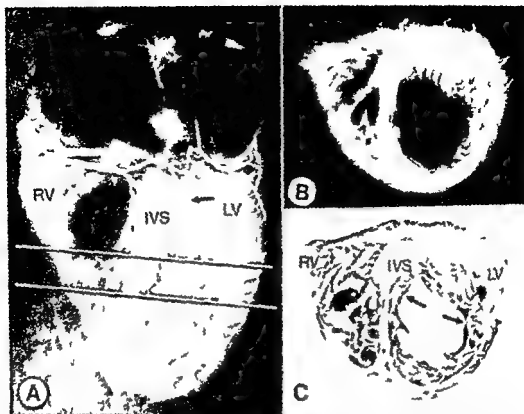


Fig 4 A through C A Postmortem coronary arteriogram The left anterior descending coronary artery is severely narrowed in its proximal portion (arrow) and its distal branches are poorly filled. The apical region of the left ventricle is expanded B Radiograph of transverse section of the heart at the level shown by lines in A The infarcted anterior septal wall is markedly thinned compared to the surviving inferior lateral wall C Cross phot graph of the same heart section shown in B The infarct margins are at the arrows The expansion of the infarct is shown by the lateral displacement of the anterior papillary muscle complex

ing a transmural myocardial infarction. Inspiration or motion often intensifies the pain, which is often exacerbated by lying flat and relieved by sitting up. Splinting and dyspnea occasionally associated with pericarditis may be misdiagnosed as increasing congestive heart failure. On auscultation a typical three component rub is often present but occasionally the rub may be heard only in systole or diastole and is misdiagnosed as a systolic or diastolic murmur or no rub is heard. Low grade fever is usually present. The chest radiograph may demonstrate an enlarging cardiac silhouette due to a pericardial effusion. The electrocardiogram may have characteristic ST segment elevation but this is often not present. Pericardial inflammation may predispose to arrhythmias.

Non-cardiac cause of chest pain or hemodynamic deterioration must always be considered. Pulmonary embolism may present with chest pain, dyspnea, increasing heart failure, fever, and

tachycardia. The chest pain of a dissecting aortic aneurysm is often localized in the posterior thorax but can present with anterior chest pain. A murmur of aortic insufficiency and a widened mediastinum are useful clues. Acute abdominal conditions must not be overlooked as an etiology of chest pain.

Our patient's presentation emphasizes the importance of a careful history in the initial evaluation of a patient with chest pain. The physical exam, electrocardiogram, and CK all may be normal. Our patient suffered a large anterior transmural myocardial infarction. The CK value probably peaked in the 36 hour interval between his initial emergency room visit and admission with the admission value of 850 IU/L on the descending portion of the CK curve.

This patient did well until the sixth hospital day when he developed chest pain associated with pulmonary congestion, a fall in his blood pressure, and prominent electrocardiographic changes. No

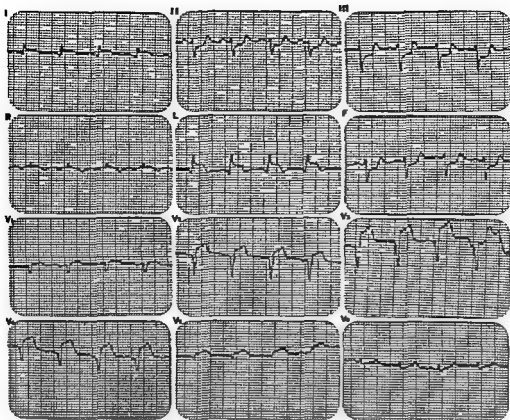


Fig 3 ECG taken during pain on day 6 reveals evolution of anterior transmural myocardial infarction as well as acute ischemic changes with more pronounced ST segment elevation anteriorly and depression inferiorly than was present on tracings taken since admission

tion Cardiac blood pool scintigraphy may also differentiate between these two conditions. Injection of a bolus of technetium labelled serum albumin into the antecubital vein or preferably into the pulmonary artery through a flow directed balloon catheter produces a dynamic nuclear angiogram. In the presence of a VSD the tracer appears in the right ventricle and pulmonary artery almost immediately after it appears in the left ventricle. If the physical findings are suggestive of cardiac tamponade a flow directed balloon catheter may confirm its presence but if the suspicion of ventricular free wall rupture is high only cardiac catheterization with demonstration of leakage of dye on the ventriculogram can confirm and localize the tear.

The reported incidence of ventricular aneurysm following a myocardial infarction varies from 3.5% to 35% due to differences in diagnostic criteria.¹¹ When defined as a protrusion of a localized portion of the external aspect of the left ventricle beyond the remainder of the cardiac surface with simultaneous protrusion of the cavity,

the incidence is much closer to the lower figure. Aneurysm formation may occur acutely within the first week of a myocardial infarction or not until several months or years following infarction. Aneurysms most frequently occur in the anterior surface of the left ventricle following transmural anterior myocardial infarctions. Inadequate bed rest following infarction has been suggested to contribute to the development of ventricular aneurysms but this has not been confirmed. Increasing congestive heart failure, serious arrhythmias and recurrent embolic phenomenon are symptoms that should raise the possibility of aneurysm formation. Palpation may reveal an abnormal precordial pulsation. Chest radiographs may have abnormal contour of the left cardiac border including a localized bulge.¹² The electrocardiogram often reveals persistent ST segment elevation. Two dimensional echocardiography is a useful non invasive technique for detecting aneurysms.

Pericarditis is a not infrequent cause of precordial or shoulder pain within the first week follow-

new murmurs were audible no abnormal precordial pulsations were described and there was no re-elevation of the CK. He had two more episodes of chest pain not associated with electrocardiographic changes or CK elevation but with persistent pulmonary congestion. He had no further chest pain after initiation of nitroglycerin ointment therapy but died suddenly 21 days after admission. The absence of any murmurs or precordial thrill makes papillary muscle dysfunction or rupture and ventricular septal rupture unlikely causes of the cardiac decompensation. Rupture of the ventricular free wall is equally unlikely for signs of cardiac tamponade should be present in a patient surviving for several days. The persistent ST segment elevation suggests the presence of diffuse hypokinesia or an aneurysm. A study of the natural history of ST segment elevation following acute myocardial infarction found that ST segment elevation persisting more than 2 weeks after myocardial infarction did not resolve over a 11 month follow up.¹¹ It was associated with clinically more severe myocardial infarctions and left ventricular aneurysm. Other than ST segment elevation there were no other signs suggestive of pericarditis.

This patient's clinical course is best explained by extension of his myocardial infarction. As noted previously further myocardial necrosis has been noted in more than 50% of acute transmural myocardial infarctions at an average of 5.8 days after admission.¹ After occlusion of a coronary artery the myocardial infarction in the distribution of the occluded vessel is not complete rather there is a zone of reversibly ischemic myocardium that is at risk for infarction.¹ During the episodes of chest pain our patient was probably extending his infarct to include these areas of ischemic myocardium despite the absence of a re-elevation of the CK. It is not clear if the nitroglycerin ointment prevented further ischemic episodes or if the infarct has been completed with no further myocardium in jeopardy. The persistent pulmonary congestion after the episodes of chest pain was secondary to extension of the myocardial injury further compromising cardiac function. Studies are now underway to develop effective techniques of identifying patients with large areas of ischemic myocardium at jeopardy in the setting of acute myocardial infarction. Interventions designed to preserve the ischemic myocardium might then successfully alter the course of patients such as the one under discussion.

Autopsy findings

The heart examined after postmortem coronary arteriography and fixation in distension¹ demonstrated severe atherosclerosis with a 90% occlusion of the proximal left anterior descending coronary artery (Fig 4). The other coronary arteries had diffuse calcified atherosclerosis but no other obstructions greater than 50% of the lumen. Histologic study of the region of maximum obstruction of the left anterior descending showed organizing thrombus situated over an ulcerated atherosclerotic plaque (Fig 5).

The region of heart supplied by the left anterior descending coronary artery had a massive transmural myocardial infarct (Figs 4 and 5). The infarct involved the epicardial fat and a portion of the right ventricle. It extended from the anterior papillary muscle group to the junction of mid and inferior thirds of the interventricular septum. The infarcted wall was markedly thinned compared to the surviving inferior and lateral wall.

Histological study of the infarct showed it to be all of one age consistent with the clinical date of infarction. The margins of the infarcted tissue adjacent to the surviving vascularized zones had well established granulation tissue formation. The midportion of the infarct which was well removed from a vascular supply showed little evidence of resolution of the necrotic tissue (Fig 5). A small area of mural thrombus overlies the endocardium in the middle of the infarct but the majority of the endocardium showed thickening by connective tissue proliferation consistent with the infarct's age.¹

The lungs were congested and edematous. Two small organizing infarcts with associated thromboemboli were present.

Pathology discussion

DR GROVER M. HUTCHINS The findings in the heart at autopsy show clearly that there had been but a single episode of myocardial necrosis. The very large transmural anterior septal infarct was produced by thrombotic occlusion of the proximal left anterior descending coronary artery. Usually in these cases the thrombus overlies an atherosclerotic plaque which has erosion or ulceration of its surface.¹² The injured plaque surface and the plaque contents exposed to the circulating blood serve as a nidus for thrombosis. Even in this patient where some time has elapsed since the acute event and organization and recanalization of the thrombus has occurred it is possible to

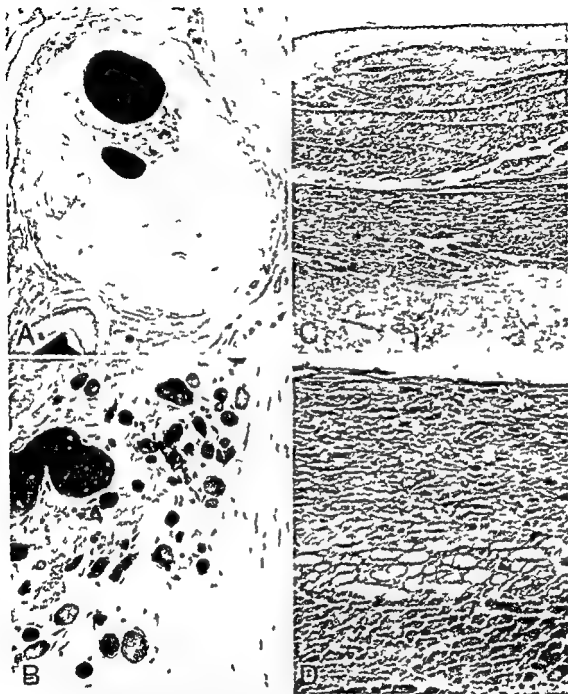


Fig 5 A through D A Transverse section of the left anterior descending coronary artery at the level of the arrow in Fig 4 A There are multiple channels of recanalization filled with black injection mass in the organizing thrombus (Hematoxylin and eosin original magnification $\times 30$) B Channel of recanalization organizing thrombus and fibrous remnants of ruptured atherosclerotic plaque from the section shown in A (Hematoxylin and eosin original magnification $\times 300$) C Transverse section of the anteroseptal transmural myocardial infarct from near its midpoint The thinning of the wall is not explainable by reparative processes which are poorly developed in the infarct (Hematoxylin and eosin original magnification $\times 70$) D The endocardium shows marked thickening by mesenchymal cells and connective tissues in the area of the infarct The surviving subendocardial muscle is markedly vacuolated The infarcted muscle cells are eosinophilic and anucleate (Hematoxylin and eosin original magnification $\times 300$)

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Pathology discussion

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recognize fibrous remnants of the atheroma in the organizing thrombus

The worsening of the patient's symptoms six days after the onset of the infarct is best explained by an expansion of the original lesion. The topography of the heart as shown in Fig 1 is consistent with this interpretation. The infarcted zone is markedly thinned compared to the adjacent surviving muscle thinned to a much greater degree than can be accounted for simply by the removal of necrotic muscle. Also the relative positions of the anterior papillary muscle has been shifted to a more lateral position. These two morphologic changes, thinning of the infarct and altered topographic relationships can be accounted for by an expansion of the infarct.

It is probable that the expansion occurs by an intramural tearing of the necrotic myocardium. Ruptures of the ventricular wall septum or papillary muscle tend to occur at 4 to 6 days post infarction. The sudden clinical worsening observed in this patient 6 days post infarction would correlate well with infarct expansion. Extension of the infarct that is additional new myocardial necrosis was not observed.

That the left ventricle develops worsened cardiac dysfunction as a result of infarct expansion even though no additional muscle has undergone necrosis may be secondary to the topographic changes. The surviving inferior and lateral myocardium suffers a loss of curvature as a result of the expansion of the anterior septal region. Effective ventricular function is dependent on an adequate thickness of myocardium arranged with appropriate curvature to translate wall tension into intracavitary pressure. Infarct expansion tends to flatten parts of the functioning myocardium rendering them less able to generate pressure.

Infarct expansion is of common occurrence in patients with large transmural infarcts.¹ In some instances the hypotension which accompanies the acute ventricular dilatation may lead to focal necroses on the margin of the infarct in the distribution of the obstructed artery. These secondary lesions probably account for the serum enzyme elevations observed in some patients with this second event. The electrocardiographic changes occurring at that time² may reflect simply an expanded area of infarct being presented to the precordial leads. The evolution of infarct expansion originally observed in the hearts of patients studied at autopsy has now been

confirmed by serial two dimensional echocardiographic studies. A higher mortality rate was observed in those patients in whom there was a greater expansion of the infarct.

Summary

This 57 year old man suffered a large transmural antero-septal myocardial infarct. After an initial stable period of several days he developed episodes of chest pain, hypotension and congestive failure. The left sided congestive failure persisted until death. Study of the heart at autopsy showed that the worsened clinical state could be explained by expansion of the area of infarcted myocardium. Infarct expansion may be regarded as a subtle form of myocardial rupture. Intramural tearing of necrotic muscle may occur abruptly or insidiously and may lead to worsened cardiac function and symptoms and signs suggestive of new infarction. The phenomenon of expansion should be distinguished from extension defined as additional myocardial necrosis since it may have important long term effects on the heart's topography and function.

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established working standards for vectorcardiography in 1970¹ but no real unanimity exists even now as to the best electrode system.

To cardiologists not primarily interested in vectorcardiography, these disagreements on lead systems have probably acted as a deterrent to clinical interest. For that reason, this review will bypass completely a discussion of the relative merits of various lead systems—allowing the reader interested in that aspect to pursue the appropriate references on his own.

A vectorcardiographic loop is produced by the simultaneous recording and combination of any two of the three leads (X plus Z, X plus Y, Y plus Z). These voltages are plotted from a central point usually on an oscilloscopic screen but in the case of the direct writing vectorcardiograph a moving arm writes the loop on an immobile piece of graph paper.

Since most electrocardiographic information is found in the X (left right) and Z (posterior anterior) directions, it is not surprising that the X-Z combination (horizontal transverse or XZ plane) has the greatest diagnostic power. The X-Y combination is designated as the frontal plane, and the Y-Z combination is designated as the sagittal plane which may be viewed from either the right or left.

Since these loops are a plot of voltage against voltage elapsed time must be indicated by interruption of the otherwise continuous recording at predetermined intervals such as 1, 2, 2.5, 5, or 10 msec each. The tracing is interrupted in such a way that each segment of the loop has a distinct leading or trailing edge, whose blunt or pointed end indicates the directional movement of the loop as a whole.

If the XYZ leads are recorded on magnetic tape, the loops may be generated later from any set of simultaneous complexes and this taped information may then be subjected also to signal averaging, noise reduction, and computer analysis, storage and retrieval.

In its simplest form vectorcardiography has many disadvantages. The superimposition of P, QRS, and T loops causes serious difficulty in evaluating and timing initial and terminal QRS forces. However, the use of gating circuits now available in the current commercially available units permits selective recording of isolated P, QRS, or T loop. Thus the overlap problem has been largely eliminated.

The high gains used in vectorcardiography readily introduce artifacts and 60 Hz interference especially in the Y axis. These problems can be generally overcome by meticulous care of electrodes and cable tips, proper skin preparation, and careful grounding of the patient and the vectorcardiographic equipment.

Location of the vectorcardiographic department far away from high voltage electrical equipment such as x-ray machines and a comfortable bed for the patient (to decrease muscle movement) are also desirable. Despite these precautions, however, occasional patients cannot be recorded without confusing interference.

Bedside vectorcardiography is eminently possible and is performed in many institutions. However, it is even more often beset with technical problems as bedridden patients may be attached to other electrical equipment which causes interference and such patients are frequently uncooperative. In addition, vectorcardiographic equipment readily breaks down, especially when moved about excessively. Probably for these reasons, vectorcardiographic study of acute ECG problems (such as acute myocardial infarction) are relatively few. Nevertheless, VCGs have even been recorded during exercise.^{4, 5}

Vectorcardiograms are commonly recorded at very high amplification (5 cm to 40 cm per millivolt). The very high amplifications are used for study of P and T loops. To the extent that the diagnostic power of vectorcardiography depends on this high amplification, which facilitates precise time and voltage measurements, equivalent results are entirely possible using standard leads with similar amplification.

The development of the corrected lead systems has encouraged quantitative analysis of the XYZ leads and of the vectorcardiographic loops. These measurements may be made manually or by computer, but the unique diagnostic power of the VCG lies in the directional and rotary characteristics of loops, the so-called phase relationships which result from the combination of voltages from the three lead axes.

This review will be largely concerned with the qualitative description of P, QRS, and T loops in a variety of clinical situations rather than with the more quantitative aspects except for some simple quantitative criteria and measurements which can be derived manually. As Witham⁶ has stated, the analysis of a VCG by an experienced

clinical vectorcardiography in adults Part 1

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The classic 12 lead electrocardiogram (ECG) remains the standard display method for surface cardiac electrical activity. Another display, the vectorcardiogram (VCG), despite an extensive literature developed over almost 30 years and the ready commercial availability of vectorcardiographic equipment is employed in relatively few institutions. Even when available it is usually employed in only a small minority of cardiac patients.

This review is directed to the cardiologist whose training and interests may not have included vectorcardiography but who may now seek an outline of current knowledge, literature and applications of this technique.

The author plans to keep constantly in mind the message implied in the paper by Eliot and associates entitled "Loops for the Lost: An Introductory Lesson for Vector Electrocardiographic Enjoyment (If not Proficiency and Accuracy)."

Several excellent sources on vectorcardiography are available in standard textbook form, programmed or atlas formats, and also in review articles and audio cassettes. The texts by Chou and co-workers, and by Cooksey and colleagues include sections devoted entirely to pediatric aspects emphasizing congenital heart disease. Published symposia include sections on surface mapping and computer analysis. This review, however, will be devoted to the current status of clinical vectorcardiography in adult patients.

The most simplistic approach to the VCG assumes that all cardiac electrical activity (P

QRS, ST and T) originates from a single point (E) located in the anatomic center of the chest and conducted homogeneously to the surface. In that situation an anatomically oriented electrode system would yield reliable X (left positive right negative), Y (foot positive head negative) and Z (posterior positive anterior negative) leads which would necessarily display all the data recordable by any surface electrode system.

Unfortunately for vectorcardiographers the heart does not behave like a simple dipole generator immersed in a sphere filled with saline. Accordingly, a variety of lead systems have been described which either ignore or correct the inhomogeneities and compartmentalizations of the human heart.

The corrected systems prescribe the location of seven or more electrodes, modify the voltages obtained by means of resistances, and then combine the modified voltages in order to produce appropriate X, Y and Z axis potentials. The correction results in a three lead (XYZ) ECG which those surface voltages would represent in a 150 pound male subject with an idealized torso.

Thus errors in correction are inherently present in large or small persons, or in those with thoracic deformities and probably also in those with cardiac enlargement. The basic assumptions also break down when the conductivity of the thoracic contents is greatly altered from the normal as in the case of emphysema.

The Frank seven electrode lead system is almost universally used presently in the United States, but serious workers have championed other systems, have compared systems to one another, and have even compared day to day variations and the effects of electrode placement in various interspaces and in various body positions and phases of respiration.^{1,2,3} A special committee of the American Heart Association

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Since these loops are a plot of voltage against voltage elapsed time must be indicated by interruption of the otherwise continuous recording at predetermined intervals such as 1, 2, 2.5, 5 or 10 msec each. The tracing is interrupted in such a way that each segment of the loop has a distinct leading or trailing edge whose blunt or pointed end indicates the directional movement of the loop as a whole.

If the XYZ leads are recorded on magnetic tape the loops may be generated later from any set of simultaneous complexes and this taped information may then be subjected also to signal averaging, noise reduction and computer analysis, storage and retrieval.

In its simplest form vectorcardiography has many disadvantages. The superimposition of P, QRS and T loops causes serious difficulty in evaluating and timing initial and terminal QRS forces. However, the use of gating circuits now available in the current commercially available units permits selective recording of isolated P, QRS or T loops. Thus the overlap problem has been largely eliminated.

The high gains used in vectorcardiography readily introduce artifacts and 60 Hz interference especially in the Y axis. These problems can be generally overcome by meticulous care of electrodes and cable tips, proper skin preparation, and careful grounding of the patient and the vectorcardiographic equipment.

Location of the vectorcardiographic department far away from high voltage electrical equipment such as x-ray machines and a comfortable bed for the patient (to decrease muscle movement) are also desirable. Despite these precautions however occasional patients cannot be recorded without confusing interference.

Bedside vectorcardiography is eminently possible and is performed in many institutions. However it is even more often beset with technical problems as bedridden patients may be attached to other electrical equipment which causes interference and such patients are frequently uncooperative. In addition vectorcardiographic equipment readily breaks down especially when moved about excessively. Probably for these reasons vectorcardiographic study of acute ECG problems (such as acute myocardial infarction) are relatively few. Nevertheless VCGs have even been recorded during exercise.^{4,5}

Vectorcardiograms are commonly recorded at very high amplification (5 cm to 40 cm per millivolt). The very high amplifications are used for study of P and T loops. To the extent that the diagnostic power of vectorcardiography depends on this high amplification which facilitates precise time and voltage measurements equivalent results are entirely possible using standard leads with similar amplification.

The development of the corrected lead systems has encouraged quantitative analysis of the XYZ leads and of the vectorcardiographic loops. These measurements may be made manually or by computer but the unique diagnostic power of the VCG lies in the directional and rotary characteristics of loops, the so called phase relationships which result from the combination of voltages from the three lead axes.

This review will be largely concerned with the qualitative description of P, QRS and T loops in a variety of clinical situations rather than with the more quantitative aspects except for some simple quantitative criteria and measurements which can be derived manually. As Witham⁶ has stated the analysis of a VCG by an experienced

observer requires only a few minutes and one or two simple measurements

The normal QRS loop (references 2 to 40)

Vectorcardiographic notation can sometimes be confusing and many different kinds of terminology are used by different workers to describe the same thing. The simplest descriptive terms are *direction* and *rotation*.

Since the horizontal or transverse loop is derived from a combination of the X (left right) and Z (posterior anterior) axes, those four directions plus the designations *clockwise* or *counterclockwise* are really sufficient for almost all descriptive purposes.

Thus it may be simply stated that in the normal horizontal plane QRS loop the earliest forces are generally right and anterior followed by counterclockwise movement left and anterior which usually is completed by 30 to 35 msec.

Then the loop proceeds left and posterior where the maximum vectors are located and still with counterclockwise rotation. The loop finally returns to the E point after terminal rightward forces are commonly inscribed posteriorly. The time dashes are frequently close together indicating slight conduction delay for the first 20 msec and the last 30 msec of the QRS loops. The duration of the loops in the normal usually does not exceed 100 msec. However with tape recording techniques and high amplification occasional normal values up to 120 msec have been observed.⁴

The maximum voltage in the horizontal plane rarely exceeds 20 millivolts in the normal. Standardization is usually inscribed as a 1 or 0.5 millivolt equivalent adjacent to each loop submitted for interpretation.

Inspection of a few normal vectorcardiograms in any of the general references will permit even a novice to familiarize himself quickly with normal loops. In the frontal (X Y) reference plane the directions are of course left right and inferior superior and the rotations are again clockwise or counterclockwise. In this plane however the normal rotation varies according to the direction of the major QRS vector. If the QRS loop lies along the X axis or close to it (horizontal position) the loop will normally exhibit counterclockwise rotation. On the other hand if the major QRS vector lies more or less along the Y axis (vertical) position the normal loop will

exhibit clockwise rotation. In the intermediate position roughly at +45 degrees in the frontal plane the loops are commonly rather narrow and may exhibit figure of eight shapes or may display clockwise or counterclockwise movement. An important variant of normal is frequently seen in the frontal plane especially in young women of slender body build. The major QRS vector may be directed along or even to the right of the Y axis producing a "vertical" position. The initial forces are commonly leftward rather than to the right and the entire loop is inscribed clockwise. The initial leftward forces are above the X axis so that Q waves are inscribed in scalar Lead I and also in Leads 3 and F of the conventional electrocardiogram. This loop is similar in some respects to loops seen in inferior divisional block and in right ventricular hypertrophy. It may also be confused on occasion with the frontal loop of inferior myocardial infarction.

When the vectorcardiographer has described the horizontal and frontal loops he has utilized information from all three (X Y and Z) axes and theoretically no additional information can be derived from the last combination (Y Z)—the sagittal reference plane.

It naturally follows from the above considerations that when the sagittal reference plane is viewed from the right the initial forces will be anterior the major forces posterior and the rotation will be clockwise.

The value of recording loops in all three projections lies in the possibility that initial or terminal forces may be perpendicular to one of the reference planes and therefore not be recorded well if at all in that particular plane.

The vast majority of vectorcardiographic interpretation however can be made from inspection and measurement of the horizontal and frontal loops only—the sagittal reference plane being used for confirmatory purposes.

Although variations in QRS loop magnitudes have been described related to sex race and body build these variations are rather small. However in an occasional case it is important to realize that voltages tend to be smaller in women and larger in males especially blacks. Greater voltage variations are encountered in the vectorcardiograms of infants children and adolescents.^{27, 28} Here the relative thinness of the chest wall plays an important role. The normal voltages for the various reference planes at different ages have

tal plane and generally exhibits counterclockwise rotation. These T loop abnormalities as well as other varieties of repolarization disorders will be discussed in a separate section devoted to T loops.

Right ventricular hypertrophy (references 2 to 16, 56 to 74)

As has been discussed above the normal QRS loop represents a J loop vectorcardiogram owing to the normal domination of QRS activity by the left ventricle. It is not surprising therefore that in only very advanced right ventricular hypertrophy will the resulting QRS loop be oriented completely anterior and rightward—the electrical position of the right ventricle. In lesser degrees of right ventricular hypertrophy a shift of the QRS either anteriorly or to the right occurs but usually with preservation of some leftward QRS forces and with preservation of the counterclockwise rotation in the horizontal plane which is characteristic of the normal left ventricular QRS loop.

These several features have become the basis of Chou and associates' classification of right ventricular hypertrophy. The classic or severe type in which the loop is oriented both to the right and anterior in the horizontal plane and with reversal of rotation from counterclockwise to clockwise has been designated as Type A. This variety is seen commonly in congenital heart disease in children especially with pressure overloads as in pulmonic valve stenosis. When seen in an adult for example with cor pulmonale or mitral stenosis one may be sure that the pulmonary artery pressure is extremely high. Type B right ventricular hypertrophy is characterized by an anterior addition of QRS forces usually in the first half of the loop and with little or no addition of rightward forces. This results in an anterior counterclockwise QRS loop in the horizontal plane which is oriented to the left and anterior of the E point. In general Type B RVH loops are encountered with milder degrees of right ventricular hypertrophy than Type A. In the Type C variety anterior forces are minimal and the major alteration from normal is the addition of rightward forces usually in the middle and terminal portions of the QRS. The normal counterclockwise rotation is preserved, and of course the addition of rightward forces decreases the maximum leftward voltage while the maximum rightward voltage increases especially terminally.

This variety of QRS loop is frequently seen in acquired right ventricular hypertrophy in adults especially in cor pulmonale and in mitral stenosis.

Although many published quantitative criteria^{4, 6, 11} are available for the identification of right ventricular hypertrophy the following have proven to be of the greatest value in the author's experience.

1 Maximum rightward voltage of 10 millivolts or greater

2 The left right millivolt ratio less than 10

3 The percentage of loop area in the right posterior quadrant of the transverse plane exceeds 20% of the total QRS loop area

4 The anterior and rightward QRS loop area in the transverse plane exceeds 70% of the total area

5 The QRS loop area in the right inferior quadrant of the frontal plane exceeds 20% of the total area

As in the case of left ventricular overload, attempts have been made to identify diastolic or systolic overloads on the basis of various VCG patterns. Two decades of experience have convinced most workers that such separations are simply not possible. In the case of pure pressure overload on the right side there is little doubt that the rightward voltages bear a close relationship to the right ventricular systolic pressure^{3, 7, 11} and may be predictive of pulmonic valve gradient in cases of pulmonic valvular stenosis. However in the frequent combinations of right ventricular obstruction with other lesions such as shunts attempts at pressure estimation are often misleading.

The greatest difficulties in the vectorcardiographic diagnosis of right ventricular hypertrophy lie in two special circumstances.

1 The counterclockwise anterior horizontal loop which may resemble the loop of dorsal myocardial infarction or a very similar loop seen commonly in persons without heart disease of any kind. This problem will be discussed in a subsequent section as anterior conduction delay.

2 The problem of loops which have some characteristics of right ventricular conduction delay (terminal slowing oriented to the right either anterior or posterior) but with significant anterior or rightward orientation of major QRS vectors. Here the separation between a pure conduction delay and conduction delay asso-

angle the distal half of the QRS loop may exceed in area the proximal half and the time at which maximum QRS forces are achieved may be delayed.¹

These vectorcardiographic features are particularly valuable when voltage criteria for left ventricular hypertrophy are not satisfied. Although values of 20 millivolts or greater in the horizontal plane are strongly suggestive in adults of left ventricular hypertrophy, such voltages are commonly not achieved even when the scalar 12 lead ECG satisfies standard voltage criteria. This discrepancy probably results in the Frank system from the attenuation of uncorrected torso voltages by the resistances employed, especially at the apical or V₁ position which frequently is the site of the greatest voltage found on the torso. Attenuation may also result when the cube or tetrahedral lead systems are used owing to the remoteness of the electrodes from the precordium.

Despite the lack of sensitivity to decreased voltage the other QRS loop characteristics of LVH described above are frequently valuable guides to diagnosis. However, it must be admitted that as far as voltage criteria are concerned the scalar 12 lead ECG is a more sensitive detector of left ventricular hypertrophy than is the vector cardiogram.

Caution must be used in interpreting high voltage QRS loops in children or adolescents. The thin chest wall and relatively large heart frequently result in high QRS voltages in the absence of anatomic abnormality. The overall QRS duration in left ventricular hypertrophy may frequently reach 120 msec but the rotational characteristics do not resemble left bundle branch block and the time dashes are evenly spaced quite dissimilar from the clustering effect seen in bundle branch disturbances.

Several studies have correlated hemodynamics and left ventricular mass with vectorcardiographic measurements.^{2,3}

Shizawa and associates² correlated the vector cardiogram with left ventricular mass determined angiographically while Bennett and Evans³ made similar correlations with echocardiographic measurements.

In both studies maximum vectorcardiographic voltages especially in the horizontal plane correlated extremely well with left ventricular mass determined, as mentioned above, Ellison and Restieaux⁴ have reviewed the correlations

between right or left ventricular hemodynamic load and the vectorcardiogram while Yankopoulos and associates⁵ made similar studies in 257 patients with clinical aortic valvular disease.

Again although many vectorcardiographic measurements were used the most effective were horizontal plane or spatial voltages and the R wave peak time in lead X.

However Yankopoulos and colleagues⁵ confirmed the difficulty of finding criteria which would separate systolic overload left ventricular hypertrophy (aortic stenosis) from volume overload left ventricular hypertrophy (aortic regurgitation).

No reliable criteria enabling separation were found and it seems reasonable at this stage of knowledge to be satisfied with the diagnosis of an abnormal QRS loop indicative of left ventricular hypertrophy or left ventricular overload without specifying whether the ventricle has been subjected to increased volume or pressure work. An additional qualitative characteristic of left ventricular hypertrophy loops is the tendency for the normal initial anterior rightward forces (found in approximately 85% of normals) to be replaced by initial anterior leftward forces. This characteristic is present in approximately 60% of patients with hypertension or aortic valvular disease. No completely satisfactory explanation for this initial shift has been established although several have been proposed. In the author's view simple early leftward posterior addition would naturally reduce or even eliminate the normal right anterior initial forces and could account for the observed changes without invoking anatomical shifts of the interventricular septum or septal fibrosis or infarction.

The frontal QRS loop in left ventricular hypertrophy is most commonly located inferior to the X axis and to the left of the E point. Thus an abnormal superior axis is not a feature of left ventricular hypertrophy. However the loops commonly lie close to the X axis and in this position as in normal loops occupying similar positions the rotation is counterclockwise. The voltage criteria for hypertrophy in the frontal reference plane is also approximately 3 millivolts especially if the patient is over 40 years of age. In younger patients a value of 4 millivolts should be exceeded in order that left ventricular hypertrophy be diagnosed.

The T loop in left ventricular hypertrophy is oriented to the right and anterior in the horizon

nor forces will include associated right ventricular hypertrophy associated dorsal infarction or associated anterior conduction delay^{10,11} and this will be discussed in a subsequent section devoted to prominent anterior forces.

When the horizontal QRS loop suggests right ventricular hypertrophy because of prominent anterior forces (Type B) or because of anterior and clockwise rotation (Type A)¹² and the frontal loop does not exhibit the expected clockwise rotation but is instead inscribed counterclockwise associated left ventricular hypertrophy should be considered.¹³ In these instances if the counterclockwise rotation in the frontal plane is associated with an abnormal superior axis right ventricular hypertrophy with associated superior divisional block or its equivalent would be the preferred diagnosis.

Ventricular septal defect in infancy is an interesting model of biventricular hypertrophy with varying degrees of right ventricular enlargement depending upon the restrictive characteristics of the septal defect. In a non restrictive defect the right ventricle operates against systemic pressure and the most severe type of right ventricular hypertrophy results. All gradations of relative right and left ventricular hypertrophy are thus possible in this entity. Riggs and associates¹⁴ have described vectorcardiographic patterns in the horizontal plane which suggest the presence of non restrictive defects. As one might expect these are the patterns of more severe right ventricular hypertrophy. In one such pattern the horizontal loop is completely anterior rightward and entirely clockwise while in the second pattern suggesting a non restrictive defect only the mid portion of the QRS loop exhibits counterclockwise rotation with the entire loop anterior to the E point the significant terminal rightward forces and a terminal appendage are inscribed clockwise.

The scalar electrocardiographic equivalent of the Katz-Wachtel phenomenon is found in the vectorcardiographic loop in the horizontal plane characteristic of left ventricular hypertrophy but with prominent anterior forces exceeding 0.6 millivolts. The scalar precordial leads in such instances would display very large biphasic complexes and are thus suggestive of biventricular hypertrophy.

Gambor and Siskin¹⁵ have compared the vectorcardiographic with the standard electrocardiograms of 87 patients. The necropsy evidence of

biventricular hypertrophy to both normals and to patients with left ventricular hypertrophy or right ventricular hypertrophy. They have published useful scalar criteria for separating the BVH cases from normal and for separating BVH cases respectively from LVH or from RVH.

Prominent anterior QRS forces (references 85 to 101)

So far in this review changes in voltage at axis shift have been described as resulting only from hypertrophy of the right or left ventricle. However as mentioned earlier in the discussion entirely similar axis shifts may occur as a result of subtraction (as infarction) or from conduction delay—in which the QRS axis shifts in the direction of the impaired conduction. One of the promises of vectorcardiography was the apparent ability to recognize true posterior or dorsal infarction.^{16,17} In such cases the subtraction posteriorly directed QRS forces would result in an anterior shift of QRS loops. Although the preordial scalar leads in such cases would continue to show R waves as they do normally the changes in precordial leads might be limited to a broadening of the R waves in Leads V₁, V₂ and V₃. In contrast the vectorcardiographic loop would show a major shift in direction anterior and the left of the F point.

As vectorcardiography developed and became more quantitative with the introduction of corrected lead systems actual quantitative criteria were proposed for the recognition of true posterior infarction¹⁸ when prominent anterior loops were encountered and were unaccompanied by evidence for inferior or lateral infarction—in which cases of course the diagnosis of adjacent dorsal infarction was relatively easy.

These concepts were proven incorrect with the advent of coronary arteriography and by contrast ventriculography.¹⁹ With these techniques it became apparent that many patients presenting with prominent anterior QRS loops had either perfectly normal coronary arteries or inappropriately placed coronary disease—most frequently in the left anterior descending artery. Clearly some other explanation was needed.

These difficulties were recognized by several authors notably by Kennedy and associates²⁰ and by Ha and colleagues²¹ who pointed out that the prominent anterior horizontal QRS loops of patients with proven dorsal infarction were in fact

ciated with right ventricular hypertrophy may be difficult indeed. The classic problem is presented by patients suspected of atrial septal defect and who present with scalar ECG's manifesting RSR complexes in Lead V and a picture of incomplete right bundle branch block. In such cases a clear separation even by vectorcardiogram between RVH and pure right ventricular conduction delay may be difficult. In the absence of terminal conduction slowing and with loops oriented largely anterior to the E point a diagnosis of moderate RVH as seen in atrial septal defect is warranted. However when only terminal conduction delay is present so that pure right ventricular conduction defect must be diagnosed atrial septal defect is by no means ruled out.

The problems attending the diagnosis of right ventricular hypertrophy in the presence of right bundle branch block will be dealt with in the section on right bundle branch block.

The frontal QRS loop in right ventricular hypertrophy of either Types A or C is oriented inferior to the E point with clockwise rotation and prominent terminal forces to the right. The Type B frontal loop lacking late prominent rightward forces may be entirely normal.

Certain vectorcardiographic changes may occur in emphysema even in the absence of significant right ventricular hypertrophy. These changes result from the overinflation of the lungs and the more vertical position of the heart resulting from descent of the diaphragms.

The electrical QRS forces tend to become oriented along the Y axis and a prominently inferior or superior axis may be observed. In addition the interposition of overexpanded lung tissue between the heart and the chest electrodes may result in a marked attenuation of the anterior QRS forces producing a picture reminiscent of anterior infarction and sometimes making that diagnosis difficult to exclude.

Thus in a vectorcardiogram presenting with decreased amplitude and duration of anterior forces coupled with an abnormally superior or inferior frontal axis a diagnosis of emphysema could logically be supported in the presence of appropriate clinical information while in the absence of such data an incorrect diagnosis of anterior infarction could easily be made. The reader is reminded of the basic assumptions of vectorcardiography referred to in the introduction. In emphysema and in chest deformities such as kyphoscoliosis these

basic assumptions—only approximations at best—break down and a qualitative descriptive approach to the QRS loops may be preferable to more quantitative analysis.

The T loop in right ventricular hypertrophy is most commonly oriented to the left and usually exhibits clockwise rotation. In the Type A loops the T loop is usually posterior and sometimes markedly so. In the Type C loop the T loop orientation may be somewhat more leftward but the clockwise rotation is usually maintained. Unfortunately for differential diagnosis by vectorcardiogram the T loops in right bundle branch block are identical to those of right ventricular hypertrophy. This problem will be discussed in the section on T loops.

The atrial vectorcardiogram is often of value when the QRS loops suggest right ventricular hypertrophy. A P loop characteristic of left atrial overload in the presence of right ventricular enlargement by VCG always suggests mitral valve disease. In contrast right atrial overload in the presence of right ventricular hypertrophy calls attention to a purely right sided problem. P loops will be discussed in a separate section of this review.

Biventricular hypertrophy (references 2 to 16 75 to 84)

Inasmuch as left ventricular hypertrophy adds left or posterior forces or both while right ventricular hypertrophy adds anterior or rightward forces or both it follows that in some instances such additions may be mutually cancellable and the resulting QRS loop may be entirely normal. In most instances however vectorcardiographic clues may suggest the presence of biventricular hypertrophy although no really firm diagnostic criteria have been established which have stood the test of time.

When the vectorcardiogram is characteristic of left ventricular hypertrophy because of high leftward voltage the presence of prominent large right posterior forces exceeding 20% of the total horizontal loop area should raise the question of the presence of right ventricular hypertrophy as well.

In a horizontal loop quite characteristic of left ventricular hypertrophy very large anterior forces exceeding 0.6 millivolts should call for additional explanation. As usual with such loops the differential diagnosis for the prominent ante-

Many perplexing problems in vectocardiography such as right bundle branch block with very prominent anterior forces or superior divisional block with prominent anterior forces are much better approached if the possibility of anterior conduction delay is kept in mind. This will often allow the vectorcardiographer to avoid the pitfall of mistaken diagnoses of associated dorsal infarction or right ventricular hypertrophy especially when the clinical picture indicates that neither diagnosis is likely.

In the following sections on conduction disorders and on myocardial infarction frequent reference will be made to the problem of prominent anterior QRS forces and the content of the present section will be assumed as standard information.

Myocardial infarction and pseudo infarction (references 1 to 16, 102 to 160)

An extensive literature on the QRS loop abnormalities resulting from myocardial infarction is available in the textbooks, atlases and symposia listed as general references in the first section of this review.¹

Useful tabulations of quantitative criteria as well as excellent diagrams of the QRS loop abnormalities in infarctions of various location may be found in the texts by Chou and associates² by Cooksey and colleagues³ and by Witham⁴ as well as in papers by Gunnar and co-workers^{10, 11} by Van Herpen and associates¹⁶ and by Eddleman and Pipberger.¹ The classic findings in infarctions of significant size are easy to recognize and little dispute exists about diagnostic criteria.^{10, 11, 12, 13, 14} The fundamental effect of an infarction is the subtraction of QRS potentials from the infarcted area resulting in a QRS shift in a direction away from the area of QRS potential loss.

This subtraction effect which is maximal in the first half of the QRS loop but may spare the initial 01 or 02 sec segment in some cases results in an unexpected bowing or convexity of the loop away from the infarcted zone.

For example in inferior myocardial infarction the first half of the QRS loop is characteristically displaced superiorly and to the left with an upward convexity away from the diaphragmatic location of the infarction. This results in a clockwise rotation of a rather transversely placed frontal loop—a marked contrast to the usual counterclockwise rotation in that electrical

position.¹ If the initial 01 or 02 sec of the QRS loop are spared by the infarction and remain directed inferiorly the upward bowing effect between 20 and 40 or 50 msec is still quite evident and the diagnosis is apparent in the VCG.

Thus the diagnosis of inferior infarction from the frontal plane vectorcardiogram can be easily established, even in the presence of R waves in Leads 3 and aV_F of the conventional scalar electrocardiogram.^{10, 11} The most useful quantitative criteria are a superior position of the 30 msec vector and an X intercept of the QRS loop located 0.3 millivolts or greater from the E point.^{11, 12}

Very similar considerations govern the genesis of the abnormal horizontal loops in anterior myocardial infarction.

Here as a result of anterior necrosis with a corresponding subtraction effect on the QRS loop the initial forces are directed posteriorly in marked contrast to the normal right and anterior position.

In anteroapical infarctions the 01 and 02 sec vectors are posterior while in more strictly anterior infarction the 01 or 02 sec vectors may remain anterior and right with subsequent posterior shift after 02 sec. Some early clockwise rotation is common. These loops which exhibit deformity after completion of the initial forces, thus are similar qualitatively to the inferior infarction loops in which the deformity develops after 02 sec.¹¹

In many anterior infarctions the normal counterclockwise rotation of the bulk of the horizontal loop is preserved. However in more extensive infarctions and especially in those with a lateral component the rotation of the loop changes to clockwise.^{1, 14, 15}

With lateral wall infarction the major change occurs in the loops which include the X axis (horizontal and frontal). The initial forces are abnormally rightwards exceeding the normal 0.22 sec duration for rightward forces.

In the case of the frontal plane these exaggerated rightward forces commonly exhibit counter-clockwise rotation (whereas in the normal such vertical forces usually rotate clockwise).

In the horizontal plane the abnormal rightward forces may be directed anteriorly if the lateral infarction is associated with dorsal involvement or posteriorly if the association is with anterior infarction.^{10, 11, 12, 13, 14} In all of these instances the changes in direction and rotation of the loops

tinguishable from very similar loops found in patients proven by invasive techniques to be free of coronary disease or right ventricular hypertrophy.

Some authors devoted themselves to establishing criteria which would distinguish between right ventricular hypertrophy and pure posterior infarction but did not attempt to separate these pathological conditions from the normal variant which was frequently encountered and which produced an identical QRS abnormality.¹⁰

Until the mid 1970s the anatomical and functional divisions of the left bundle branch were generally considered as hemi divisions with the left bundle presumably dividing into a superior anterior branch and an inferior posterior branch. Rosenbaum and colleagues¹¹ introduced and popularized the concept of electrocardiographic hemiblock as well as the concept that the entire intraventricular conducting system formed a trifascicular system when the right bundle branch was included along with the two subdivisions of the left bundle branch.

The term hemiblock unfortunately implies that no room is left for other divisions or fascicles. However the anatomic work of Demoulin and Kulbertus¹² and others has established that the anatomic structure of the left bundle branch instead of two equal divisions is extremely variable and most often includes a third anterior or septal fascicle. Although great variation was encountered in the anatomic dissections of left bundle branch systems performed by Demoulin and Kulbertus¹² it was apparent that this anterior fascicle was sometimes a direct extension of the left main bundle sometimes a branch of the superior fascicle and sometimes a branch of the inferior fascicle.

Thus an anatomic basis was laid for the concept that anterior conduction delay might be the cause for some of the puzzling instances of prominent anterior QRS loops in the demonstrated absence of right ventricular hypertrophy or of coronary disease with true posterior infarction.¹³

Convincing evidence that this is indeed the case has come from two directions. The first has been the production of prominent anterior QRS forces with atrial stimulation with the aberration disappearing at slower heart rates. In these experiments which have been reported by three sepa-

rate groups of investigators (Kulbertus and associates¹⁴, Cohen and colleagues¹⁵ and Reiffel and Bigger¹⁶) other types of aberration such as right bundle branch block, superior divisional block, etc. were also produced at different coupling intervals. Although Reiffel and Bigger entitled their paper: Pure anterior conduction delay: A variant fascicular defect, they do not attribute the delay to a disorder of conduction in any specific new fascicular subdivision but Kulbertus and colleagues¹⁴ believe that impaired conduction in the septal fascicle is indeed the cause for the observed aberration and anterior shift of the QRS.

Hoffman and co-workers¹⁰ have described prominent anterior QRS loops in patients whose only coronary pathology was in the anterior descending artery. In two such cases following unsuccessful coronary artery bypass surgery, anterior myocardial infarction developed with a complete loss of the pre-existing prominent anterior forces. In the cases reported no coronary disease of vessels supplying the posterior wall or ventricular contraction defect of the posterior wall was observed.¹⁷

It thus seems more than reasonable that at least in some cases prominent anterior forces may result from a conduction disorder probably in the anterior or septal fascicle of the left bundle branch as well as from right ventricular hypertrophy or from true dorsal myocardial infarction. This concept is important because prominent anterior forces may be encountered combined with bundle branch block, fascicular block, myocardial infarction or ventricular hypertrophy. It becomes necessary therefore to consider anterior conduction delay as the possible mechanism for prominent anterior forces whenever it is encountered—not only when it occurs in the pure form which originally led to the overdiagnosis of true posterior myocardial infarction. The concept of anterior conduction delay is supported by additional logical force. Since it is well known and accepted that conduction delay may shift the QRS to the right (right bundle branch block) to the left and posterior (left bundle branch block), superiorly (superior divisional block) or inferiorly (inferior divisional block) it would seem unreasonable that shift in an anterior direction could not occur just as easily, especially as strong anatomic evidence for anterior fascicles has been presented.

cardiomyopathies pulmonary emphysema and both left and right ventricular hypertrophies. These causes of pseudo infarction in the vector cardiogram will be discussed separately.

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is dramatic and obvious and with a little practice, expertise can be achieved by any cardiologist familiar with standard electrocardiographic diagnosis and with the normal appearance of QRS loops as described previously.

These rather standard vectorcardiographic abnormalities have been correlated with clinical diagnoses of myocardial infarction (based on ECG criteria and enzymatic measurements) with coronary arteriography and ultimately with contrast ventriculography as well.^{1, 11, 13, 14, 15, 17} In general rather good correlations have been observed between the classic loop abnormalities described above and with appropriately located coronary artery obstructions and areas of ventricular asynergy and akinesia.^{13, 17, 18} In a study of 102 consecutive patients whose right anterior oblique left ventriculograms showed severe asynergy in the anterior and apical segments 84 presented with horizontal QRS loops characteristic of anterior infarction but with clockwise rotation in the horizontal plane.¹ In another study patients with inferior myocardial infarction presenting with unexpectedly low ejection fractions were found by vectorcardiography to present additional evidence for anterior infarction not apparent in the standard 12 lead scalar ECG.

Thus it seems possible that some correlation of the vectorcardiogram with infarct size and with residual myocardial function can be made although it appears likely that such correlation will be crude at best. In experimental infarction with serial vectorcardiograms available direct approximations of infarct weight have been possible although this is seldom a situation which permits clinically.

Much more difficulty is present in the analysis of the distal half of QRS loops especially the importance of small distortions called bites. Normally the QRS loops are inscribed smoothly and without sudden changes in rotation. The earliest workers in vectorcardiography correlated distal bites with autopsy evidence of myocardial scarring¹ and a theoretical basis for the phenomenon was developed by Selvester and colleagues¹ who constructed a computer model for the normal vectorcardiogram and were able to show that subtraction of small segments (as little as one % of the total) would result in bites similar to those observed clinically. Distal abnormalities have been correlated with infarctions in the diaphragmatic surface.

The clinical vectorcardiographer fortunately will usually encounter such bites when the proximal portion of the QRS loops exhibits classic deformities characteristic of infarction as described above. The real difficulty lies when such bites are detected in the absence of more proximal abnormalities. Witham has suggested that before significance is attached to such deviations they be identified in at least two planes have a minimum duration of 45 msec and a minimal deviation of 0.1 millivolts.

Such bites are almost never found in normal young subjects but in contrast are fairly common in patients with angina, hyperlipidemia, diabetes and hypertension. Witham's text includes a valuable tabulation of distal QRS loop abnormalities resulting from infarctions in all areas.

Although the available literature indicates rather good correlations between the vectorcardiogram and clinical autopsy, arteriographic and ventriculographic evidence of myocardial infarction many difficulties nevertheless remain. The problem of large anterior loops which may result from true posterior infarction has already been discussed. However it should be pointed out that the diagnosis of true isolated posterior infarction is really quite unusual. Generally posterior infarction is associated with inferior or lateral infarction and the combination is easy to recognize.^{11, 12} The vectorcardiographer should be wary when the *only* abnormality found is an anterior QRS loop as the patient may be entirely free of coronary disease, his QRS loop representing anterior conduction delay as previously discussed.

Horizontal QRS loops with prominent anterior forces are easily recognized as they are displaced into the left anterior quadrant of the horizontal reference plane. Certain quantitative descriptors may be used to identify these loops.¹² The anterior voltage measured on the Z axis reaches 0.5 millivolts or greater. The half area vector is ten degrees or more anterior to the Y axis and maximum anterior forces are achieved at 30 msec or later. In addition the total duration of anterior QRS forces exceeds 42 msec. Unfortunately identical quantitative characteristics are found in patients with anterior conduction delay and dorsal infarction so that the differential diagnosis cannot be made on the basis of the vectorcardiographic characteristics.

Myocardial infarction may be mimicked by a variety of cardiac disorders the most common are

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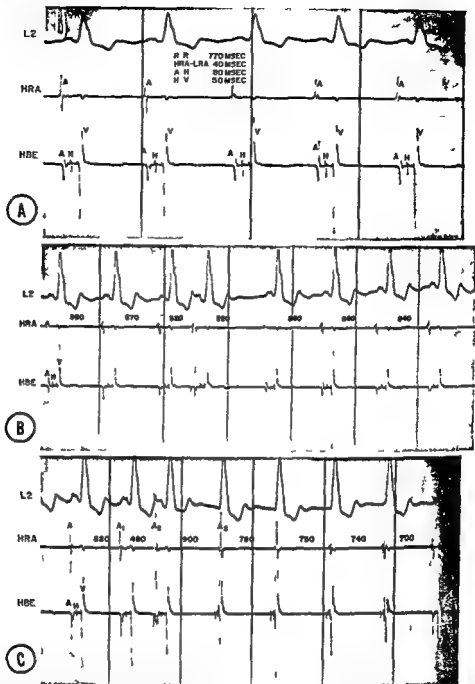


Fig 1 (Patient 5) The effect of atropine on the sinoatrial node. From the top down Lead II, right atrial electrogram (HRA), His bundle electrogram (HBE). **A** the PR subintervals are normal except for an increase in the HRA LRA interval to 40 msec. **B** an artificial premature beat is followed by a full compensatory pause. **C** after administration of 10 mg of atropine the atrial premature beat is followed by a full compensatory pause which is terminated by an AV junctional rhythm at a slightly slower rate than the sinus rhythm. The last beat is a fusion between the sinus and AV junctional beat.

of the sinus node occurred simultaneously in this patient. However, it should be pointed out that there are also other explanations for the paradoxical effect of atropine on the automaticity of the sinus node as previously discussed.⁵

b Atropine in the evaluation of ischemic heart

disease. Cokkinos and associates¹² showed that higher ventricular rates induced by atrial pacing after the administration of atropine led to an increase in ST segment depression and the incidence of angina pectoris in patients with angiographically proved CAD.

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Julian Frieden

The effect of atropine on cardiac arrhythmias and conduction Part 2

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II Diagnostic use of atropine

Sinus node dysfunction The nonspecific nature of the clinical symptoms caused by sinus node dysfunction and the low sensitivity of the electrophysiological findings indicate a need for additional tests to facilitate the diagnosis of sinus node dysfunction.²⁹⁻³¹ Atropine may satisfy this need.³²

In patients with sinus bradycardia caused by sinus node dysfunction, atropine in doses of 1 to 2 mg does not increase the sinus rate by more than 10 to 15 beats/minute and never over a rate of 90/minute.³³ On the other hand, when sinus bradycardia is caused by extracardiac factors, atropine exerts a marked positive chronotropic effect. This use of the drug in the diagnosis of sinus node dysfunction has been recently challenged by Dighton, who was not able to confirm this difference in the response to atropine.³⁴

Atropine produces sustained AV junctional rhythm in some patients with sinus node dysfunction. Although this arrhythmia developed in a small number of patients with symptomatic sinus node dysfunction, its occurrence will support the diagnosis of sinus node dysfunction. Two unusual effects of atropine on sinus node recovery time may further aid in the diagnosis of this disorder: Paradoxical prolongation of the sinus node recovery time³⁵ and the replacement of sinus rhythm by AV junctional rhythm when atrial pacing is

suddenly stopped also substantiate the diagnosis.

The possibility of improved sinoatrial conduction and unmasking of abnormal sinus node automaticity after the administration of atropine is suggested in the following patient. A 72-year-old woman with a history of paroxysmal atrial fibrillation was hospitalized because of syncope. The ECG showed sinus rhythm and LBBB. The resting electrophysiological measurements were normal except for a high low right atrial interval, which was prolonged to 40 msec (normal 20 msec) (Fig 6A). Atrial premature beats introduced before the administration of atropine did not reset the SA node regardless of the coupling interval (Fig 6B). This finding was consistent with a first degree SA block.⁴ Administration of atropine accelerated the heart rate from 69/minute to 88/minute. During measurement of sinoatrial conduction time, atrial premature beats introduced in late diastole (89% to 96% of the spontaneous sinus cycle) were followed by a full compensatory pause (Fig 6C). However, the sinus node was suppressed and the return rhythm was AV junctional after atrial premature beats with a shorter coupling interval. The AV junctional beats occurred following the expected full compensatory pause. The mechanism underlying this effect of atropine is not clear, but we believe that because atropine abolished the sinoatrial conduction disturbance, the premature atrial impulses penetrated into the sinus node and suppressed it. This mechanism is similar to the one which was used for the explanation of the paradoxical effect of atropine on the sinus node recovery time.³⁶⁻³⁸ If our hypothesis is correct, then an abnormal automaticity and conductivity

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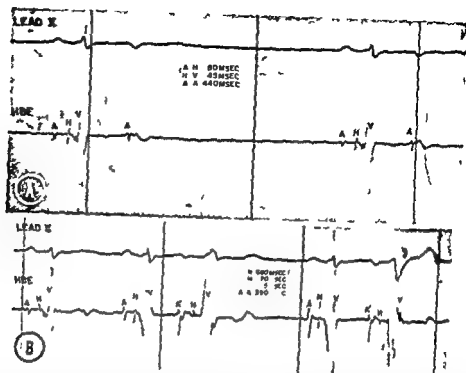


Fig 8 (Patient 7) The effect of atropine on atrial premature beats A Lead II and His bundle electrogram (HBE) show sinus beats alternating with blocked atrial premature beats B following administration of 0.5 mg of atropine the sinus rate accelerates and the conduction through the AV node improves permitting the conduction of atrial premature beats The QRS complexes of the atrial premature beats are wide because of aberrant conduction

only for patients in the coronary care unit but also prior to hospitalization for patients with acute myocardial infarction."

Subsequently experimental findings¹⁰ and case reports¹¹ challenged the routine use of atropine in patients with acute myocardial infarction and asymptomatic bradycardia. First it was shown that atropine itself may increase ventricular irritability¹² and that increased vagal tone is not necessarily harmful in experimental myocardial infarction¹³ or in patients with myocardial infarction¹⁴. At the same time Epstein and co-workers pointed out that while atropine suppresses so-called benign ventricular premature beats it is less effective in the therapy of malignant ventricular premature beats. The effect of atropine on hypotension was also questioned. Finally the possible adverse effect of increased heart rate on the size of myocardial infarction also came into consideration. In other words uncontrolled tachycardia caused by atropine may increase the size of the infarct and this led to doubts about the usefulness of the drug.

The possible adverse effect of atropine and the experimental findings noted above suggested a

need for re evaluation or redefinition of the role of atropine in managing patients with acute myocardial infarction. Despite a number of contradictory recommendations we believe that the use of atropine in acute myocardial infarction is still justified^{15,16} and it remains the drug of choice for patients in whom sinus node suppression is complicated by hypotension or increased ventricular irritability. The drug is not indicated however for uncomplicated sinus bradycardia and should probably not be given without medical supervision. Because the adverse effects of atropine are dose related¹⁷ it is important that the dose of the drug be kept between 0.4 and 0.8 mg. It has been shown by Chadda and colleagues¹⁸ that 10 patients with acute myocardial infarction doses of 0.8 mg or less are usually not associated with increased ventricular irritability. Unanswered however is the question whether patients who do not respond to lower doses of atropine should be treated by insertion of a temporary pacemaker or with increasing doses of atropine. At this time we prefer to use a temporary pacemaker in these nonresponsive patients.

The clinical effectiveness of atropine in

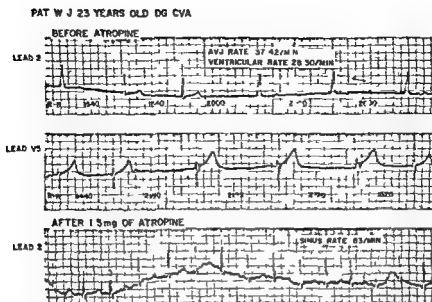


Fig 7 (Patient 6) The effect of atropine on the sinoatrial node. Leads II and V recorded before the administration of atropine show a slightly irregular AV junctional rhythm with alternating idioventricular beats. After the administration of atropine a sinus rhythm resumes.

c Normalization of Wolff Parkinson White syndrome. Since the original description of the Wolff Parkinson White (W P W) syndrome it has been known that atropine can restore a normal QRS complex in some patients with this syndrome. This effect is unpredictable however.¹⁴ Normalization of W P W syndrome after atropine occurs in subjects in whom the drug facilitates conduction through the AVN and decreases the ERP of the AVN. Refractoriness and conduction through the AVN become shorter than through the accessory pathway and therefore activation of the ventricles occurs by way of the normal pathway. This effect is of clinical significance mainly in patients with suspected myocardial infarction. The ECG of W P W syndrome not only simulates myocardial infarction but also masks the presence of an acute myocardial infarction. Normalization of the QRS complex therefore reveals information of diagnostic value in patients with suspected myocardial infarction and the W P W syndrome.

III Therapeutic indications for atropine

a Sinus node dysfunction: Administration of atropine is indicated in patients with sudden onset of sinus node suppression complicated by hypotension or increased ventricular irritability. The indication for atropine is less certain in patients with chronic symptomatic sinus node

dysfunction. It is possible that atropine or other long acting parasympatholytic drugs may be of some benefit in patients in whom for any reason a permanent pacemaker is not implanted.

The effects of atropine in a patient with marked suppression of the sinus node is seen in Fig 7. The patient was a 23 year old man admitted to the hospital in deep coma because of a ruptured subarachnoid aneurysm. There was no SA node activity and the AV junctional rate was 37/minute to 42/minute (Fig 7). Intermittent suppression of the AV junctional pacemaker occurred causing an idioventricular rhythm. Administration of 1.5 mg of atropine restored a regular sinus rhythm.

■ Myocardial infarction. During the past few years attitudes about the use of atropine for its effect on the heart rate in patients with acute myocardial infarction have been revised several times. Atropine was recommended in acute myocardial infarction and sinus bradycardia because slow heart rate was associated with hypotension and increased ventricular irritability¹⁵ and the beneficial effects of atropine on hypotension and ventricular arrhythmias were confirmed in the majority of clinical studies.¹⁵ In addition atropine was also used prophylactically to accelerate the heart rate in patients with bradycardia but without hypotension and ventricular irritability. Use of the drug for bradycardia was suggested not

adverse effects in acute myocardial infarction initiated a series of investigations in which the arrhythmogenic effects of atropine were intensively studied, especially as mediated through the parasympathetic nervous system. That the autonomic nervous system is in a state of imbalance early in the acute stage of myocardial infarction was stressed by Webb and co-workers.⁹ While some studies demonstrated that vagal stimulation increases the ventricular fibrillation threshold in dogs with acute myocardial infarction,¹⁰ other studies suggest that the effect of the vagus on the ventricular fibrillation threshold can only be demonstrated on the normal myocardium and not on the ischemic myocardium.¹⁰⁰ Kolman and co-workers¹⁰¹ believe that the beneficial effect of the vagus nerve in stabilizing ventricular irritability depends on the level of adrenergic activity, with vagal effects becoming apparent only if there is concomitant increased activity of its sympathetic counterpart.

Reviewing the adverse effect of atropine in acute myocardial infarction we found that the only factor which was important in the pathogenesis of ventricular arrhythmias in man was the acceleration of the heart rate after atropine. An increased heart rate almost always preceded the appearance of increased ventricular irritability. The localization of the infarct, the age of the patient or the time of administration of atropine did not seem to play an important role in the pathogenesis of ventricular arrhythmias after atropine, although tachycardia was more likely to appear after higher doses of atropine. This relationship is shown in the next illustrative case.

A 72 year old patient was seen one hour after the onset of severe chest pain. The blood pressure was 70/50 mm Hg and the ECG showed marked sinus bradycardia (20/minute to 34/minute), first degree AV block and an acute inferior myocardial infarction (Fig 9A). Administration of 0.5 mg of atropine did not influence the sinus rate. Following a second 0.5 mg dose of atropine the sinus rate accelerated to 130/minute (Fig 9B). The sinus tachycardia was associated with increased ST segment elevation and was followed by ventricular tachycardia and ventricular fibrillation (Fig 9C and D). Defibrillation was successfully carried out and the patient made a good recovery (Fig 9E). This case demonstrated that atropine induced ventricular irritability is preceded by acceleration of the sinus rate and sup-

ports the observation that at least 10 mg of atropine is necessary for the adverse effect of the drug.

Summary

The effects of atropine on various components of the specialized conduction system of the heart and the myocardium itself are reviewed. These actions are sometimes unpredictable or paradoxical depending on the component showing the dominant effect and the health of the entire system. Atropine is best known for its chronotropic effect. Improved sinoatrial conduction has been demonstrated but the effect on the refractoriness of atrial muscle is unsettled. Atropine stimulates the atrioventricular (A-V) junctional pacemaker and facilitates conduction through the A-V node. The response of the subjunctional portion of the specialized conduction system to the drug is unpredictable and controversial in some respects.

Atropine is useful in the diagnosis of sinus node dysfunction in the evaluation of coronary artery disease during atrial pacing and in attempting to produce normal conduction in patients with the Wolff-Parkinson-White Syndrome. Its principal therapeutic application is in correcting the hypotension bradycardia syndrome occurring during acute myocardial infarction. It also has a role in the temporary management of sinus node dysfunction. Atropine may also cause arrhythmias including atrial fibrillation, A-V dissociation, ventricular tachycardia and ventricular fibrillation. The clinical settings in which atropine may be arrhythmogenic are discussed.

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patients with myocardial infarction complicated by AV conduction disturbances is i.e.s certain Atropine may improve second and third degree AV block in patients with either inferior or anterior myocardial infarction²⁴ but this effect on AV conduction is unpredictable We also believe that because of the variability of the response to atropine and the possible adverse effects of the drug a temporary pacemaker is the therapy of choice if the AV block causes hemodynamic deterioration or ventricular arrhythmias

IV Adverse effects of atropine

Until recently the adverse effects of atropine on the cardiac rhythm were thought to be infrequent and of little clinical significance Because atropine is now used more frequently than it was in the past we have become more aware of the implications of atropine induced complications In addition the drug is often administered to patients with acute myocardial infarction and unstable cardiac rhythm which is probably another cause of the higher incidence of adverse effects of atropine Most of the undesired effects of atropine are self limited and except for serious ventricular arrhythmias do not themselves require therapy The use of smaller doses of atropine in patients with acute myocardial infarction is probably the best way to avoid these complications

The adverse effects of atropine on the heart were extensively reviewed through 1970 by Scherf and Schott²⁵ Atrial fibrillation induced by vagolytic drugs was reported by Orninus in patients with acute myocardial infarction Supraventricular tachycardia after atropine was discussed earlier²⁶

The occurrence of ventricular premature beats or ventricular tachycardia after administration of atropine in patients without cardiac disease is rare Dauchot and Gravenstein²⁷ who studied the effect of atropine on the cardiac rhythm in 79 patients showed that the drug caused ventricular premature beats in one older patient On the other hand simultaneous administration of atropine with halothane and cyclopropane which are myocardial depressants may lead to serious ventricular arrhythmias even in patients without heart disease

The following case shows a possible pseudo adverse effect of atropine A His bundle recording from a 68 year old woman with a history of

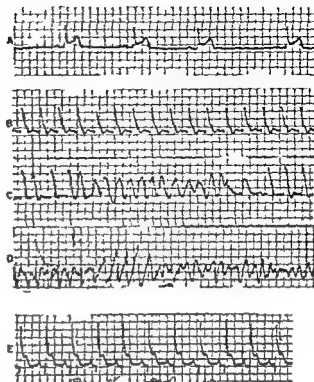


Fig 9 (Patient 8) Atropine-induced ventricular fibrillation in a patient with acute inferior myocardial infarction A lead II shows sinus bradycardia (25-34/min.) PR interval of 0.2 second and ST segment elevation B following the administration of 10 mg of atropine the sinus rate accelerates to 130/min This is associated with an increase in the ST segment elevation C D ventricular tachycardia and ventricular fibrillation then appear E sinus rhythm is restored by defibrillation.

syncope is shown in Fig 8 The ECG revealed sinus rhythm frequent atrial premature beats some blocked and others with aberrant ventricular conduction His bundle recording confirmed the blocked atrial premature beats which were the cause of the bradycardia (Fig 8A) Administration of 0.5 mg of atropine did not abolish the atrial premature beats but improved the AV conduction so that all the atrial premature beats were now aberrantly conducted (Fig 8B) Blocked atrial premature beats are readily recognized on 12 lead ECG's because the atrial deflection can be identified at least in some of the leads However if only a single monitor lead is analyzed as is usually done in the CCU the identification and diagnosis of nonconducted APC's may be difficult Had this patient been monitored with a single lead the appearance of APC's after atropine might have been erroneously interpreted as an adverse effect of the drug

The wide use of atropine and its potential

Of right ventricular congestive heart failure

Selected pathophysiologic aspects of left ventricular congestive heart failure were discussed previously but right ventricular congestive heart failure (RVCHF) was not considered in detail in these discussions. The same general arguments that apply to the left ventricle (LV) the left pump of the heart also apply to the right ventricle (RV) the right pump of the heart. However there are specific differences. For example there are essentially 100 cc of blood in the pulmonary blood vessels and 4,500 cc in the systemic blood vessels when the heart is normal and fully compensated and each ventricle is pumping the same volume of blood and the two pumps are well synchronized. For illustrative purposes if it is assumed that each ventricle pumps 100 cc per stroke and the heart rate is 100 beats per minute and if all things remained equal the volume of blood in the pulmonary and systemic circulations would remain stabilized at 100 and 4,500 cc respectively for the pulmonary and systemic vascular systems. However if the right ventricle were to fail slightly and pump 99 cc of blood per stroke while the left ventricle continued to pump 100 cc per stroke each minute 100 cc of blood would be removed from the pulmonary circulation and pumped into the systemic circulation. The pulmonary circulation would become relatively empty or "dry," and the volume of blood in the systemic circulation would increase—a volume increase which the systemic veins could readily accommodate provided they are not "tightened" by sympathetic nervous system activity. But regardless of how small the total pulmonary blood volume becomes the volume of blood within the pulmonary vessels is always equal to the volume of the lumina of the pulmonary vessels; thus the pulmonary vessels, especially the pulmonary veins would become relatively loose as the hoop tension of the wall reduced unless the tone of the smooth muscles in the walls of the vessels actively increased by means of autonomic nervous system activity. If all of the blood from the lungs (500 cc) was displaced into the systemic circulation, the systemic circulation could readily accommodate the 500 cc just as it so readily accommodates a 100 cc blood transfusion.

But as is well known clinically with right ventricular congestive heart failure (RVCHF) the neck veins become distended and the patient develops systemic venous hypertension, edema, ascites, pericardial and pleural effusion, etc. Why do these pathophysiologic manifestations occur? The abnormal non-synchronized state of the two pumps (RV and LV) results in the clinical state of RVCHF with the increase in tone (constriction) of the systemic veins as described previously. Why and by what mechanism this increase in α and β -adrenergic sympathetic tone of the systemic blood vessels occurs are not known. The clinical and physiologic

data indicate that this increase in sympathetic tone or activity does occur. The mechanisms by which water and electrolytes are subsequently retained are also not known. The water and electrolyte retaining pathologic mechanisms must be related in large part to alteration in renal function (not renal disease), as noted before, resulting from dysfunction of the two cardiac pumps. The increase in sympathetic tone could initiate physiologic phenomena which could produce the well known renal dysfunction of CHF responsible for the accumulation of edema fluid.

Surely in less than 5 minutes the left ventricular stroke volume would have to decrease to the stroke volume of the RV but the volume of blood in the pulmonary circulation could remain reduced. It could slowly return to normal levels by means of readjustments in the stroke volume of the two ventricles and readjustments of the vascular, renal, autonomic nervous system dysfunction, etc. But if the original factor which caused the RV to reduce its stroke volume in the first place were still present one can only wonder if the sympathetic (α and β) tone would return to normal even if the volume of blood in the pulmonary vessels returned to the normal level of 500 cc.

This discussion of CHF illustrates again what great difference in the state of circulation could be produced by only 1 cc stroke volume difference between the two cardiac pumps. One can readily calculate the rates of change in the circulations that could be produced by any reasonable differences in stroke volume for the two pumps and at different heart rates.

Furthermore is there such a clinical state as RVCHF with normal LV function, i.e. RVCHF without LVCHF? Theoretically it could exist with "pure" or strict pulmonary stenosis, such as with a congenital defect or in cor pulmonale.

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ALPHA ADRENERGIC ACTIVATION

BETA ADRENERGIC INHIBITION

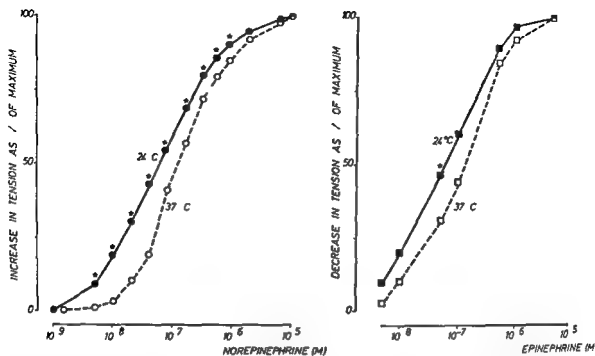


Fig 2 Demonstration that in cutaneous vessels moderate cooling augments the responsiveness of the vascular smooth muscle cells to both the alpha and beta adrenergic effects of catecholamines. The experiments were performed on isolated rings of canine saphenous veins. Left: the rings were made to contract with increasing concentrations of norepinephrine throughout the experiment neuronal disposition of norepinephrine as well as beta adrenergic receptors are blocked by the appropriate pharmacological agents. Cooling from 37 (○—○) to 24°C (●—●) shifts the dose response curve to norepinephrine to the left; the maximal contractile answers to the catecholamine were not significantly different at both temperatures (Data from Ref. 9). Potentiation by local cooling is also obtained during sympathetic nerve stimulation. Right: the rings were first made to contract with acetylcholine in the presence of phentolamine to block alpha adrenergic receptors; the relaxation caused by increasing concentrations of epinephrine was then investigated at 37°C (□—□) and 24°C (■—■). Cooling markedly facilitates the inhibitory effect of epinephrine. Similar augmentation by moderate cooling of the beta adrenergic responsiveness has been described for isoproterenol and norepinephrine. * = value at 24°C significantly different from that at 37°C ($P < 0.05$ Student's *t* test).

ents the arterial and venous responses to sympathetic nerve stimulation. The enhanced arteriolar constriction limits the amount of blood flowing through the skin. The augmented vasoconstriction directs the venous return to the deep venae cavae which run alongside the deep arteries. Unlike cutaneous vessels, deep vessels dilate when they are exposed to the colder blood coming from the skin. Thus, this favors the counter-current exchange of heat which warms up the venous blood returning to the body core. The augmented response of cutaneous blood vessels to sympathetic nerve activity during moderate cooling is due to two factors (Fig. 1): first, lowering the temperature delays the disappearance of the adrenergic neurotransmitter from the junctional cleft between the adrenergic nerve endings and the cutaneous vascular smooth muscle because it inhibits neuronal uptake, enzymatic degradation, and diffusion of norepinephrine. Thus, the amount of transmitter in the vicinity of the alpha adrenergic receptors of the vascular effector cells increases. Further, moderate cooling greatly augments the responsiveness of the cutaneous vascular smooth muscle to norepinephrine (Fig. 2 left) because the affinity of their alpha adrenergic

receptors significantly increases; this increase in affinity holds not only for norepinephrine but also for alpha adrenergic antagonists. At the same time, moderate cooling augments the sensitivity of the vascular smooth muscle for the beta adrenergic effects of catecholamines, which in normal conditions presumably tempers the increased responsiveness to the alpha adrenergic effect of these substances (Fig. 2, right).

It is tempting to assume that in primary Raynaud's disease the vasospasm associated with exposure to cold involves the local potentiating effect that temperature has on the cutaneous vasomotor response to sympathetic nerve activation, and in many instances is only an exacerbation of the physiological mechanism. The importance of the autonomic nervous system in providing the initiating signal for vasoconstriction is illustrated by the observations that the onset of the symptoms is frequently related to situations where emotional stress augments the sympathetic outflow to the cutaneous vessels, and that reserpine or sympathectomy may alleviate the symptoms.¹¹ However, the abnormality is primarily a dysfunction of the vascular smooth muscle cells, since epi-

Thermosensitivity of cutaneous vessels and Raynaud's disease*

Raynaud's disease is characterized by prolonged spasm of the digital arteries of the hand when they are exposed to a cold stimulus particularly when the subjects are emotionally upset. The exact mechanism underlying the vasospasm is unknown.

Thermoregulatory needs are the main determinants of cutaneous blood flow. Hence the sympathetic outflow to the cutaneous arterioles, arteriovenous anastomoses, and veins is continuously adjusted by the hypothalamic thermoregulatory

center. When the body temperature increases the sympathetic outflow to the skin blood vessels decreases and the sweat glands are activated and produce kinins as a result the arterioles, the arteriovenous anastomoses, and the veins open. Large amounts of blood are shunted to the latter which act as a capacious radiator for the physical exchange of heat. When the body temperature decreases, the sympathetic outflow to the skin is augmented, sweat secretion is inhibited and the dissipation of heat is restricted. Besides thermoregulatory adaptations, the skin vessels participate in homeostatic reflexes and in the cardiovascular response to emotional stress.

Local cooling (from 37°C to about 15°C) greatly aug-

Presented at the meeting of the Belgian Angiological Society on January 13, 1979.

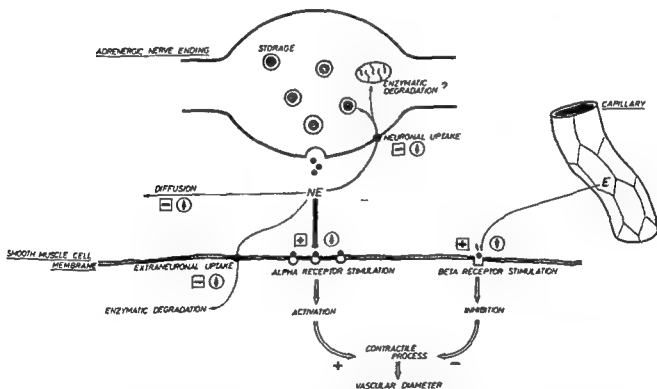


Fig 1 When the sympathetic nerves are active, cooling affects both the adrenergic nerve ending and the vascular smooth muscle cell in cutaneous vessels. The release of norepinephrine from the adrenergic nerve ending is most likely not affected by moderate cooling. Neuronal uptake and enzymatic degradation of norepinephrine are depressed by moderate cooling as well as by diffusion of the neurotransmitter out of the junctional cleft. This partially explains the increased constriction upon cooling in densely innervated cutaneous vessels since the concentration of the adrenergic neurotransmitter increases in the vicinity of the effector cells. In addition, more norepinephrine binds to the alpha adrenergic receptor sites at lower temperatures, leading to greater activation of the contractile process and thus to increased constriction of these vessels. The potentiating effect of cold is partly offset by the facilitation of the beta adrenergic effects of the catecholamines. NE = norepinephrine, E = epinephrine. □ = effect of temperature, ○ = contractile response, + = augmentation, - = depression.

disturbances in blood flow may be responsible for clinical manifestations in BMLS and the condition has been called an ischemic cardiomyopathy at the Montreal Heart Institute ' on account of an unduly large LV mass in relation to coronary blood flow

These abnormal findings have not always been confirmed when other investigators have applied the same tests to their groups of MLP patients ' However it is very difficult in this situation where the index entity is common and the clinical spectrum wide to be sure that studies with disparate results have compared like with like Measurement of LV function in the intact human heart is problematical and the frequent coexistence of mitral regurgitation and LV wall motion abnormalities in patients with MLP coming to catheter study ' adds to the methodological difficulties A drawback of thallium imaging of myocardial perfusion is its rather poor resolution a particularly unfortunate feature when the supposed abnormalities must be in the small arteries beyond the resolution of standard contrast cineangiography Moreover myocardial uptake of thallium is not purely flow-dependent and if as Selwyn and associates have stated regional disturbances in myocardial perfusion can be identified with this indicator only when metabolic abnormalities affecting cellular uptake are present it follows that those MLP patients with stress scintigraphy defects have disturbed myocardial cellular metabolism Thus it is prudent to consider the extant reports of myocardial dysfunction and perfusion abnormalities in BMLS with realistic caution

Opportunities for direct examination of myocardial tissue obtained at necropsy from subjects with BMLS are not common and no distinctive abnormality has been recognized ' Only recently have techniques of biopsy during cardiac catheterization made it possible to obtain endomyocardial tissue samples safely during life and it is of great interest that the two studies so far published ' have both presented evidence of myocardial abnormality in BMLS The report from Stanford done in 1978 ' is of right ventricular biopsy by a technique refined in cardiac transplantation follow up studies and carried out in 14 patients with BMLS Light microscopy revealed an increase in endocardial and interstitial fibrosis in eight cases Electron microscopy in 11 cases showed mitochondrial degenerative changes usually marked or severe in all and definite myocyte degeneration in four Nuclear chromatin clumping and intracellular edema were more prominent in BMLS biopsies than in control specimens obtained at transplantation from 10 normal donor hearts The inevitable criticism of this important study is that the tissue from the right side of the interventricular septum may not be representative of the myocardium beneath the prolapsing mitral valve

Left ventricular tissue is accessible for percutaneous transarterial biopsy and a method by which a bioprobe can be speedily and repeatedly be passed via a Teflon long sheath to obtain multiple endomyocardial biopsies has been described in detail With experience in developing this technique and an established laboratory dedicated to the analysis of biopsy specimens obtained during open heart surgery we were able at St Thomas Hospital London to address in a direct and novel fashion the question of abnormality of the LV in BMLS patients undergoing cardiac catheterization Endomyocardial LV biopsies from 11 patients with MLP distressing chest pain little or no mitral regurgitation and normal coronary arteries were examined by cellular chemical and biophysical meth-

ods ' Comparison was made with biopsies from a good LV control group in which normal LV function was judged by seven or eight indices and from a bad LV control group in which these indices were markedly abnormal Histochemical findings in the MLP biopsies ranged from normal to very abnormal and on a semiquantitative rating of over all histochemical abnormality the MLP group were significantly worse ($p < 0.001$) than the good LV controls and also worse than the bad LV controls but not significantly so The results for monoamine oxidase (MAO) activity reflecting ability of myofibrils to metabolize catecholamines were particularly poor with eight of the 11 MLP specimens showing abnormal MAO activity compared with 11 of 21 in the bad LV and only two of eight in the good LV group The ability of muscle fibers in unfixed biopsy sections to respond to the standardized stimulus of adenosine triphosphate (ATP) plus ionic calcium was measured in terms of alteration in birefringence of the myofibrils believed to be brought about by ATP mediated orientation of myosin molecules ' The birefringence response to ATP was markedly impaired in tissue from MLP patients with the group results in a position between the good LV and bad LV controls and significantly different from both The clear distinction ($p < 0.005$) between the good LV controls and the MLP group suggests a distinct abnormality of muscle function in the latter for this birefringence method has been shown capable of regenerating myocardial deterioration during cardiopulmonary bypass Such evidence of abnormal muscle function in this subgroup of patients with MLP and chest pain is of particular importance because it has been obtained by a method independent of the problems of assessing myocardial function in the intact ventricle

The myocardial biopsy evidence from Stanford and London ' strongly supports the concept of a diffuse abnormality of the myocardium in those patients with BMLS in whom symptoms have been sufficiently prominent to warrant cardiac catheterization It is difficult to refute use of the term cardiomyopathy in this situation Because of the major role of catecholamines in myocardial contraction the MAO abnormalities could well be part of the fundamental defect responsible for impairment of the birefringence response to ATP in the specimens from MLP patients The beta adrenergic blocking drug propranolol has acquired a reputation for usefulness in treating chest pain and other symptoms in BMLS and there may be some link between the histochemically demonstrable MAO abnormalities and this clinical impression No theory to explain the chest pain of BMLS has yet gained general acceptance ' but the cellular abnormalities to which the biopsy data now testify surely point to a metabolic/biochemical mechanism as the most likely explanation Further investigation of the pathophysiology and treatment of BMLS are now indicated and will be particularly welcomed by those in clinical practice who struggle with the management of patients with severe non anginal chest pain and without any demonstrable cardiac abnormality except MLP

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sodes of vasospasm still can be induced by exposure of the fingers to cold after sympathectomy. In patients where the phenomenon is primarily due to hypersensitivity of the alpha adrenoceptors to the sensitizing action of cooling, therapeutic effects are obtained with alpha adrenergic blocking agents. It is to be expected from the studies on isolated blood vessels that the vessels exposed to the cold will be particularly susceptible to alpha adrenergic blockade and thus that doses of blocking agents may be used which have little effect on general hemodynamics. Raynaud's disease sometimes is successfully treated with beta receptor stimulating agents. Treatment with beta adrenergic blocking agents induces Raynaud's phenomenon. Raynaud's disease is relatively frequent in patients suffering from hypothyroidism. In the animal, beta adrenergic sensitivity decreases with age a process which can be reversed by administration of thyroid hormone. These different observations all imply that Raynaud's disease could be due to a relative lack of beta adrenergic sensitivity of the cutaneous vessels. This then would exaggerate the augmentation by local cooling of the vasoconstrictor response of these vessels to the alpha adrenergic effect of the catecholamines.

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Myocardial mysteries surrounding mitral leaflet prolapse

Excessive bulging of one or both leaflets of the mitral valve has proved to be a remarkably common disorder but the hearts of subjects with such valves have not readily yielded up their secrets. Certain symptoms notably chest pain and palpitation mysteriously associated with mitral leaflet prolapse (MLP) have prompted investigation of the state of the left ventricle (LV) as well as the mitral valve itself in the symptomatic primary form of the disorder designated billowing mitral leaflet syndrome (BMLS) by Barlow and Pocock in their recent Editorial in this JOURNAL.

Suggestive evidence of a myocardial abnormality in patients with MLP has been obtained by a variety of means. Crude indications of LV dysfunction in terms of elevated resting LV end-diastolic pressure (LVEDP) an abnormal rise in LVEDP and/or cardiac index on exercise or a failure to lower LVEDP appropriately in response to atrial pacing, have been reported. Abnormal myocardial lactate metabolism has been documented in four studies. Reports from Toronto and Milwaukee of 201 thallium myocardial perfusion imaging defects on stress testing have fostered speculation that local

Table 1 Effects of venesection on hematocrit blood viscosity and general blood flow in chronic lung disease

| | Normal | Before venesection | After venesection | P |
|-------------------------|-------------|-----------------------|----------------------|---------|
| Hematocrit (%) | 43.3 ± 7.1 | 59.6 ± 6.8 | 43.9 ± 2.2 | < 0.005 |
| Viscosity (CPS) | 4.06 ± 0.36 | 5.83 ± 0.46 | 3.80 ± 0.05 | < 0.005 |
| Supratentorial CBF† | | 32.2 ± 5.2 | 57.3 ± 14.6 | < 0.005 |
| Subtentorial CBF† | | 50.7 ± 11.0 | 63.8 ± 31.4 | NS |
| Hemispherical mean CBF† | | 38.3 ± 5.1 | 60.2 ± 20.1 | < 0.025 |

Values expressed as mean ± SD
Blood viscosity obtained at shear rate 225 sec⁻¹ (Centipoise)
†Cerebral blood flow (CBF) units are expressed as mL/100 g/min
NS = refers to non-significant p value greater than 0.05

cell production increases relatively linearly with decreases in hemoglobin oxygen saturation

However in patients with lung disease where arterial carbon dioxide tension may be abnormal leading to respiratory acidosis or alkalosis there is a less well defined relationship between the degree of hemoglobin unsaturation and the red cell mass than is characteristically seen in normal subjects at altitude. It has been suggested that patients with chronic lung disease have an attenuated bone marrow response or that red cells have a decreased life span which could contribute to the variable red cell mass in lung patients compared to normals at altitude. Another factor which could result in a lower red cell mass for a given degree of arterial unsaturation is the increased cardiac output seen in some patients with chronic lung disease. With a higher cardiac output the delivery of oxygen to various tissues is increased and if intrarenal oxygen sensors responsible for the erythropoietin response were exposed to a normal oxygen supply then it is understandable why some patients would not have secondary polycythemia in spite of decreased arterial blood oxygen saturation.

Although increased red cell mass improves the oxygen carrying capacity of blood it also increases blood viscosity which tends to impede blood flow. Since blood with its particulate matter is not a Newtonian fluid its viscosity increases with increases in red cell concentration. The shape of individual red cells also affects viscosity and shape changes leading to elevated viscosity occur in hypoxic and hypercapnic blood. Because of differing metabolic rates in individual tissues blood viscosity could be quite different in individual vascular beds. Also viscosity is affected by vascular geometry and by the rate of blood flow. Controlled changes in hematocrit and blood viscosity have been shown to affect the resistance to flow in the pulmonary and peripheral circulations. The clinical significance of increased viscosity on pulmonary vascular resistance is controversial since both improvement in and no significant change in pulmonary vascular resistance have been reported following a reduction in hematocrit by venesection.

The clinical management of secondary polycythemia is not generally agreed upon. Although symptomatic improvement in mental acuity, vitality and breathing ability has been volunteered by patients whose polycythemia was treated by venesection, objective data on the mechanisms producing these symptomatic changes are sparse. Venesection does not

alter measured pulmonary function although work capacity has been demonstrated to improve.

The most direct way of reducing red cell mass is by venesection. It reduces both the red cell mass and the blood volume in cardiac failure due to cor pulmonale and it has been advocated as a preventive measure against the recurrence of cardiac failure after compensation. A consensus of opinion has arisen that venesection is of doubtful value expected to reduce the incidence of thrombotic complications noted when the red cell mass is increased.

We measured cerebral blood flow with xenon 133 before and after venesection in six chronic hypoxic pulmonary disease patients with polycythemia. We demonstrated that venesection increased cerebral flow and that the increase appeared to be preferentially greater to the cerebral cortex (Table 1). We did not correct the cerebral blood flow values in Table 1 for changes in partition coefficient resulting from changes in hemoglobin concentration because there is uncertainty about the actual tissue blood xenon 133 partition coefficient in the living brain. It is known that this coefficient increases with decreases in hemoglobin concentration and use of the correction factor would result in our measured pre-venesection cerebral blood flow values being lower than those shown. Therefore venesection to correct secondary polycythemia actually results in a larger increase in cerebral blood flow than that reported in Table 1.

The improved flow to the cerebrum could explain the symptomatic improvement noted by these patients and might also explain the improvement in blood gas values or pulmonary artery pressure (as judged from the distribution of pulmonary blood flow) changed significantly in them.

Venesection has been shown to increase cerebral blood flow in patients suffering from primary polycythemia with or without cerebrovascular accidents. Cerebral blood flow has also been demonstrated to increase in association with the general improvement noted on recovery from ruptured cerebral aneurysms. It would appear that optimal blood flow occurs at a physiological hematocrit of 45%.

A less direct approach to achieve a lower hematocrit and to reduce pulmonary artery pressure is by administration of continuous oxygen which has been found to be clinically beneficial in patients with polycythemia secondary to hypoxemia. There is a reduction in hematocrit in about 6 weeks and a decreased incidence of hospitalization due to cor pulmonale. In patients with severe hypoxemia this therapeutic

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Management of secondary polycythemia with hypoxic lung disease*

Although hypoxemia resulting from chronic lung disease is a common medical condition it is relatively uncommon to see polycythemia associated with these lung disorders. The polycythemia secondary to hypoxemia is mediated by increased erythropoietin production but erythropoietin levels and

therefore red cell mass can also be increased in the presence of certain tumors and renal disorders.

The increase in red cell mass is a beneficial physiological adjustment to hypoxemia since more oxygen can be carried in each milliliter of blood for a given arterial oxygen tension. Because of the shape of the oxygen dissociation curve there is not a dramatic decrease in the oxygen saturation of hemoglobin and therefore oxygen content of blood until oxygen tension falls below about 65 mm Hg. It is interesting that red

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Toxic polyneuritis and toxic hepatitis related to long term perhexiline maleate therapy

To the Editor

In the article "Assessment of perhexiline maleate in angiographically proven intractable angina" by M Afzal Mir (AM HEART J 96 350 1978) some side effects of the drug are reported such as tremor, dizziness, nausea, though not severe enough to impair the general condition of the patient. However, in a few cases serious side effects have been observed indicating liver and nervous system damage, with anatomical toxic hepatitis, segmentary demyelination of the peripheral nerves and decreasing of proprioceptive reflexes, pallesthetic deficit and visual impairment.

We have recently observed extremely severe liver and peripheral nerve impairment in a 51 year old male patient who had been taking perhexiline maleate (PM) at the following dosages: 600 mg daily for 1 month, 400 mg daily for the next 3 months and 200 mg daily for a further 16 months.

Symptoms of peripheral neuropathy appeared during the last 3 months of treatment, namely peripheral tingling of the four limbs, weakness of the four limb muscles (mainly of the legs), impairment of the flexion and extension movements of the feet, of the flexion and abduction movements of the thigh and impairment of the fine movements of the fingers with muscular hypotrophy. Furthermore, he was complaining of headache, dizziness, waddling gait with pallesthetic deficit, visual impairment and bilateral papilledema. The physical examination demonstrated a large and hard liver with an edge 4 cm below the costal margin (not previously observed) and physical findings of peripheral neuropathy. The SGOT was 100 IU, SGPT was 60 IU and alkaline phosphatase 11 IU.

On electromyogram (EMG) examination a slight reduction of motor unit recruitment on voluntary contraction was observed in the extensor muscles of the forearms and in the small muscles of the hands. In the lower limbs a moderate motor unit reduction was observed distally, more evident in the muscles of the anterior compartment of the legs. Motor conduction studies performed in ulnar, median, deep peroneal and posterior tibial nerves showed a severe slowing with a marked time scattering of the motor responses. These findings were in agreement with a peripheral neuropathy in which segmental demyelination was likely to be the main feature. The conduction velocity of peripheral sensorial and motor nerves showed the values in Table I.

The ECG showed inferior fibrosis and ST-T abnormalities but the typical perhexiline maleate changes were absent.

The clinical picture was interpreted as a severe peripheral neuropathy associated with toxic hepatitis, probably drug induced. Four months after discontinuing the treatment with PM, the papilledema was markedly reduced, the gait was almost completely normal, there was a mild improvement of the lower limb proprioceptive reflexes, and a mild muscular atrophy was still present.

Table I

| | Actual velocity | Normal velocity (range) |
|----------------------------------|-----------------|-------------------------|
| Median nerve | 29.2 M/sec | 57-71 M/sec |
| Ulnar nerve | 31.7 M/sec | 53-73 M/sec |
| Sciatic internal popliteal nerve | 29.8 M/sec | 40-55 M/sec |
| Sciatic external popliteal nerve | 13.8 M/sec | 40-57 M/sec |

Two months later the EMG showed a dramatic improvement of the neural conduction speed, liver enlargement however was still present and hepatic enzymes were elevated (SGOT 56 IU, SGPT 28 IU) several months after discontinuing the drug. The severe neurological lesions may be due to the presence of an undiagnosed liver disease, primary secondary to perhexiline maleate, leading to a storage of fat in the liver and in the neural tissue. The former hypothesis seems to be more likely, since in a group of five patients with normal liver function who had been taking PM in small large doses, conduction abnormalities of the peripheral nerves have not been observed.

We can conclude that liver function must be assessed before long term PM therapy is begun, while clinical signs of hepatic and peripheral nerve involvement should be carefully looked for during treatment.

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regimen may be inadequate to reduce the hematocrit to a physiological range because arterial oxygen saturation may remain decreased in spite of increasing the inspired oxygen concentration

This study of cerebral blood flow and polycythemia indicates that venesection to a physiological hematocrit may be beneficial for patients with secondary polycythemia because of apparent improvement in central nervous system function mediated by improved cerebral perfusion. Venesection should perhaps be repeated until the hematocrit reaches an optimal level of 45%. Continuing examination of the effect of rheological alteration on regional flow to all body organs should be pursued.

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propafenone. No patient had received antiarrhythmic drugs. We do not think that data from this latter group had a noticeable value in the context of our report and for this reason we had omitted relating them.

We are aware that verapamil can reveal a latent sick sinus syndrome or induce hypotension because of this (as previously stated in our Letter) we avoided using the drug in patients with sinus bradycardia or systolic blood pressure lower than 90 mm Hg. Although these seem to be logical precautions we have never observed undesirable side effects.

With regard to the possibility that the disappearance of ventricular premature beats (VPBs) had taken place spontaneously instead of being a drug effect we think that unlikely since rapid disappearance of VPBs occurred in 85% of the patients, also the lack of relapses for at least three hours after drug injection can hardly be considered fortuitous. When VPBs are treated with a bolus of lidocaine in most cases it is necessary to prolong the infusion of the drug thus suggesting that VPBs of acute myocardial infarction are not always transitory. Moreover many reports prove that the effect of verapamil given as a bolus intravenously is not attenuated completely in 10 minutes but show that the pharmacological effects of the drug last longer—thus suggesting a longer half life and/or a preferential myocardial uptake and binding of verapamil.

Finally we would like to make some comments about Dr Ahmad's statement that verapamil has no value in the control of ventricular arrhythmias. We too for a long time were convinced of this and have considered (and still do) verapamil the drug of choice in the treatment and prophylaxis of paroxysmal supraventricular tachycardia. However the increasing experimental evidence that arrhythmias following acute myocardial infarction can be related to the slow response action potentials led us to verify the usefulness of a

drug (such as verapamil) which inhibits slow responses in treatment of VPBs of acute myocardial infarction. Our results are positive and support the hypothesis that in man VPBs of acute ischemia are also related to the slow inward current.

The distinction of ventricular arrhythmias on the basis of the activating current seems to us to be a very important advancement in arrhythmology.

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Reply

To the Editor

In our series there were no serious side effects, mainly because it was a short term study and none of the patients took perhexiline maleate for more than six weeks. Serious neurological complications have been observed among those who have taken perhexiline on a long term basis, as happened in the case reported here by Dr Carruzzo and colleagues. These workers suggest that neuropathy may be due to liver disease in patients taking perhexiline. In our series serum transaminases were raised in about 30% of patients and other workers have reported abnormal liver function tests in 10% to 17% of patients, whereas the incidence of neuropathy is about 0.1% in patients taking perhexiline. Subclinical neuropathy indicated by abnormal electrophysiological measurements, occurs in two thirds of patients—a substantially higher proportion of patients than those who develop clinically recognizable neuropathy. It is obvious that abnormal electrophysiological tests and abnormal liver function tests do not help in finding the patients at risk for developing the neurological syndrome. The only way one can guard against such serious complications is by seeing the patients every month or six weeks, by examining them for serious loss of weight, questioning closely for early symptoms of neuropathy (i.e., numbness, tingling etc.) and by repeating liver function tests. Most workers would agree that the drug should be stopped if a patient continues to lose weight, develops early signs of neuropathy or if liver function tests deteriorate or remain persistently abnormal.

An early withdrawal of perhexiline is important since most of the complications caused by this drug are reversible.

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Verapamil therapy

To the Editor

A recent Letter to the Editor by Fazzini and associates warrants further comments. They state that 28 patients with myocardial infarction who presented with frequent ventricular premature beats (VPBs) in the first 48 hours of their illness were treated with intravenous verapamil. They failed to

mention these patients' ages, any concomitant therapy or any other associated disease.

Rosing and colleagues have recently reported a 77 year-old woman who developed sinus arrest and hypotension following one 80 mg oral verapamil capsule. It is noteworthy to stress that this patient had manifested no findings that would have been suggestive of sick sinus syndrome.

Verapamil, given as a bolus intravenously has a very short half life and its effect is attenuated completely within 10 minutes. It is therefore not clear whether the disappearance of VPBs up to three hours after verapamil was due to the effect of this drug or occurred spontaneously.

Systemic hypotension and prolongation of PR interval are the commonest side effects of verapamil. I strongly believe that this drug has no place in the management of VPBs of acute myocardial infarction. Furthermore verapamil appears to be of no value in the control of ventricular arrhythmia. Verapamil depresses the sinus discharge rate, therefore it is contraindicated in patients with sinoatrial disease which usually may be found in the older population. Of course verapamil is the drug of choice in the treatment and prophylaxis of paroxysmal supraventricular tachycardia.¹

Finally I should emphasize that verapamil should not be used within 48 hours after administering beta adrenergic blockers, disopyramide or quinidine therapy. Physicians caring for patients with cardiac arrhythmia should bear in mind the possible drug interactions and side effects of verapamil and be more selective in choosing patients for treatment with this agent. Nevertheless the introduction of verapamil will constitute a very significant advance in cardiovascular therapeutics in this country.

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Reply

To the Editor

We wish to thank Dr Ahmad for his observations. The age of our patients ranged between 40 and 65 years; the mean age was 58 years. Systemic hypertension was present in nine patients and diabetes mellitus was present in four. Fifteen patients had received nitrates and 20 had received

Announcements

Eighth Annual Cardiac Symposium

The Department of Medicine and Cardiac Rehabilitation of Georgia Baptist Medical Center will present its Eighth Annual Cardiac Symposium in Atlanta on October 10, 1980. The guest lecturer will be William Kannel, M.D., Co-directors of the symposium are Gerald F. Fletcher, M.D., and John H. Cantwell, M.D. For further information, contact Gerald F. Fletcher, M.D., Director of Internal Medicine, 300 Boulevard N.E., Atlanta, Ga. 30312.

Joint Conference on Stroke and Cerebral Circulation

The Stroke Council of the American Heart Association, in association with the Cerebrovascular Surgery Section of the American Association of Neurological Surgeons, The Canadian Stroke Society, of the Canadian Heart Foundation and The Society for Vascular Surgery will present a Sixth International Joint Conference on Stroke and Cerebral Circulation at the Century Plaza Hotel in Los Angeles on February 12 through 14, 1981. The conference is an open meeting, whose purpose is to provide a common forum for the presentation of material relating to all aspects of cerebrovascular disease and the physiology and pathology of the cerebral circulation. Abstracts dealing with the clinical or experimental aspects of the pathogenesis, diagnosis, medical and surgical management of vascular disease of the brain and spinal cord are welcome. Deadline for the receipt of abstracts is August 29, 1980 (postmarked). Accepted abstracts will be published in the January, 1981 issue of the journal *Stroke* of the American Heart Association.

Guidelines and further information may be obtained from Administrator Postgraduate Programs, American Heart Association, 7320 Greenville Ave., Dallas, Texas 75231. Telephone (214) 750-5441.

Cardiac Imaging and Cardiovascular Radiology

A course entitled "Cardiac imaging and review of cardiovascular radiology for residents and fellows," will be presented April 1 through 4, 1981, at the Islandia Hyatt House in San Diego, California, by the Faculty of the Department of Radiology of the University of California, San Diego Medical Center. Program Director is Michael J. Kelley, M.D. For further information, contact Mary J. Ryal, Radiology, P.O. Box 2300, La Jolla, Calif. 92038. Telephone (714) 459-9787.

Lucien Dautrebande Pathophysiology Prize for 1979

The Professeur Lucien Dautrebande prize for 1979 in the amount of \$37,000 has been awarded to Professor J. E. Desmedt, Director of the Brain Research Unit, Faculty of Medicine of the University of Brussels, Brussels, Belgium. Dr. Desmedt has been chosen by an international jury for his original contributions to neuromuscular diseases, to the mechanisms of voluntary motor control in man, and to brain mechanisms studied by the evoked potentials method in relation to maturation, aging, neurological disorders, and cognitive performance. After receiving the Dautrebande prize from the hands of H.M. Queen Fabiola of the Belgians, Dr. Desmedt emphasized in his acceptance speech the increasing importance of the systems approach of pathophysiology and of the development of physiological methods applied to man.

The next competition for the Dautrebande Prize will be held in 1982 and the award will be approximately \$48,000. All particulars may be secured by writing to Dr. Stalport, President, 30 chaussée de Liège, 5200 Huy, Belgium. For consideration in the 1982 competition, all papers must be received before December 15, 1981.

Society of Nuclear Medicine Meeting

The Eighteenth Annual Meeting of the Society of Nuclear Medicine will be held in September 1980 in Erlangen, Nurnberg, W. Germany. The main theme of the meeting is "Nuclear Medicine with its Interdependencies," with special reference to cardiology and hepatogastroenterology. For further information, contact Prof. Dr. F. Wolf, 18th International Annual Meeting Society of Nuclear Medicine, Institut und Poliklinik für Nuklearmedizin der Universität Erlangen-Nurnberg, Krankenhausstrasse 12, D-8500 Erlangen, W. Germany. Telephone 09131/853411, 153416.

Book reviews

Ambulatory ECG Monitoring Edited by Shlomo Stern M.D., F.A.C.C., London and Chicago 1978 Year Book Medical Publishers, 197 pages.

This small book edited by Stern and with several contributors reviews the technique and problems associated with applications of the technique of ambulatory monitoring. The book is clinically oriented. The 14 chapters review very well many problems related to Holter monitoring. The use of the monitor in the evaluation of arrhythmias, effects of therapeutic agents and the results of cardiac management are clearly discussed. The book describes thoroughly and very well the application of Holter monitoring. The illustrations are good and the book should be available to all cardiologists and other physicians who use ambulatory monitoring. This is a good book but it does not represent a critical discussion of the limitations, applications, and abuses concerned with Holter monitoring.

Progress in Cardiology Vol. 7 Edited by Paul N. Yu M.D. and John F. Goodwin M.D., Philadelphia 1978 Lea & Febiger 228 Pages. Price \$17.00

This is the seventh volume of the *Progress in Cardiology*. The subjects discussed vary widely in the field of cardiology. They include discussions of embryology, the role of the nervous system in cardiovascular control, emotions, catecholamines and the electrocardiogram, diet, drugs and pulmonary hypertension and angina pectoris, new operations for congenital cardiac anomalies and recent advances in peripheral vascular disease. The eight chapters are written for the clinician and housestaff in training in internal medicine and cardiology. This is another good volume and the subjects discussed are not only interesting but important.

Dynamic Cardiac Auscultation and Phonocardiography By Abner J. Delmar M.D., F.A.C.P., F.A.C.C. and Emanuel Stein M.D., M.P.H., F.A.C.P., F.A.C.C., F.C.C.P. Philadelphia 1979 W. B. Saunders Company 1023 pages. Price \$35.00

This is an atlas of over one thousand pages of excellent illustrations of simultaneous recordings of heart sounds, apex cardiograms, phases of respiration and a reference ECG. Carotid pulse tracings are included in most of the illustrations. The associated text is clearly written and the legends are quite helpful. Readers will find this to be an excellent review of phonocardiography. Page 181 contains an interesting illustration of a mid systolic click which does not occur in mid systole but rather in late systole. This illustration for example clearly indicates the looseness of nomenclature and definition of findings. The Whoop or Honk is nicely

illustrated on page 183. The book is very good. The illustrations are excellent. This book should be of value to all cardiologists, internists and trainees in internal medicine and cardiology. Careful and thoughtful study of this book should improve every clinician's cardiac auscultation.

Advances in Cardiology: New Approaches in the Diagnosis and Management of Cardiovascular Disease Edited by John H. K. Volz Basel, 1979 Harger AG, 139 pages Price \$3.50

This issue of *Advances in Cardiology* is concerned with both diagnosis and treatment. The many contributors review effectively noninvasive techniques, use of positron-emitting radionuclides, use of propranolol and newer antihypertensive drugs, pharmacologic treatment of patent ductus arteriosus, diuretic, medical and surgical management of unstable angina, surgical treatment of congenital heart disease and other important cardiovascular problems. The respective short reviews were presented at the Ninth Cardiovascular Conference held at Snowmass. The presentations are interesting and should prove of considerable value to cardiologists as well as to non-cardiologists. The subjects discussed are timely, such as the results of medical and surgical management of unstable angina.

Coronary Artery Disease: Recognition and Management By Charles E. Rackley M.D. and Richard O. Russell Jr. M.D., New York 1979 Futura Publishing Company 439 pages Price \$33.00

This book, edited by Rackley and Russell with 14 additional contributors, reviews very well the contemporary approach to the diagnosis and management of coronary artery disease. The 15 chapters include discussions of the natural history of coronary artery disease, precordial movement, echocardiography, radionuclide studies, exercise testing, clinical syndromes of coronary artery disease, coronary arteriography, cardiac catheterization, use of nitrate myocardial metabolism, bypass surgery, diagnosis and management of acute myocardial infarction. The illustrations are good and a useful bibliography is provided. This is a good review of many important aspects of the diagnosis and management of coronary artery disease. It is rather interesting that the role of electrocardiography is neglected in the considerations, whereas the newer more complex procedures are given prominent exposure. This book should be of interest to readers who are interested in learning the role of these newer procedures in cardiology. Readers will find this a useful book, especially housestaff and trainees in cardiology.

Books received

Functional Evaluation and Rehabilitation of Cardiac Patients Edited by Paolo Rossi, M.D. Chicago 1979 Year Book Medical Publishers, Inc. 384 pages Price \$37.50

Cardiovascular Physiology for Anesthesiologists By Ronald J. Gordon, Ph.D., Mark B. Ravin, M.D. and George R. Daroff, M.D. Springfield Ill. 1979 Charles C. Thomas Publisher 709 pages Price \$19.75

Shock Trauma Manual By William Gill M.D., and William H. Long M.D., Baltimore 1979 The Williams & Wilkins Company 283 pages. Price \$18.00

Pediatric Cardiology By Courtney L. Anthony M.D., Rica G. Aron, M.D., and Charles W. Fitch, M.D. Garden City N.Y., 1979 Medical Examination Publishing Co., 534 pages. Price \$16.50

etc.) cardiovascular symptoms (exertional chest pain, dyspnea and leg pain), socio-personal characteristics (educational level, consumption of alcohol, coffee, etc.), metabolic and miscellaneous features (cholesterol, uric acid, leukocyte count, forced vital capacity, etc.).

The results obtained were essentially consistent for all race-sex groups. Smokers who later quit (ex-smokers) showed statistically significant differences from smokers who continued the habit in a number of cardiovascular symptoms, socio-personal characteristics and metabolic and miscellaneous traits. In the 288 comparisons made with persistent smokers, the ex-smokers at index examination were statistically different in 130 or 15% at the $p < 0.05$ level, and the majority of these (84) were significant at the $p < 0.01$ level. Controlling for smoking quantity had little effect on the observed differences between the persistent quitters and persistent smokers. Furthermore, at index examination (when still smoking), the ex-smokers' characteristics were not very dissimilar from those of nonsmokers. Thus, the investigation clearly indicated that ex-smokers are not a representative sample of smokers with regard to their CHD-related characteristics or the extent of the smoking habit. And, most importantly, the nature of the differences revealed that smokers destined to quit (ex-smokers) showed characteristics at baseline indicative of lower CHD risk than smokers destined to continue.

The findings of our study prompt the following conclusions. The observational studies referred to above, which show lower CHD rates for ex-smokers than for continuing smokers, are flawed, having failed to observe the basic principles of valid scientific inference. Their comparisons of the CHD outcomes of the two groups are biased since they have made the false assumption that ex-smokers are representative of continuing smokers except for the change in the smoking habit. With ex-smokers self-selected to begin with and at lower CHD risk at baseline, it is small wonder that their CHD outcomes in these widely publicized studies are found to be lower than those of continuing smokers. The extent to which the CHD outcomes are lower than those of continuing smokers resulting from baseline differences remains to be determined.

The results of our new study have received strong support from the American Heart Association in their recently published report on a randomized

controlled trial of smoking cessation in middle-aged English male civil servants at high risk of cardiorespiratory disease. After almost eight years of follow-up, they found no significant differences in mortality rate between the intervention group and the normal care group, despite the greater cigarette smoking cessation (58% at 3 years) in the intervention series than in the normal care group (14% at 3 years). The authors state: "the interpretation of these observational studies is not straightforward for men who stop smoking are not a representative sample of smokers; comparison of the two groups is biased; the reversibility of the risk of cigarettes to the smokers' life may have been overestimated in observational studies. Disappointingly, we find no evidence at all of any reduction in total mortality."

What are we then to believe about the effect of stopping smoking on the risk of CHD? Despite the conventional view that cessation of smoking reduces the risk of mortality from heart disease, there is now evidence that the comparisons of the CHD outcomes between ex-smokers and smokers in the observational studies are biased and unreliable. Our new study reported above indicates that ex-smokers at baseline are at lower CHD risk to begin with, thus contributing to their eventual lower CHD outcomes. In addition, the results of the first randomized controlled trial of the possible effect of smoking cessation in middle-aged men have shown no improvement in their rate of mortality relative to those who were not urged to stop smoking, thus the reversibility of the claimed risk of cigarettes to the smoker's life has not been demonstrated. Accordingly, it is reasonable to believe there is no proof that stopping reduces the risk of heart disease.

Surgeon General's Report—1979

The second event bearing on the question of smoking and CHD is the publication of the Surgeon General's 1979 Report on Smoking and Health. The 1979 Report summarizes its views on smoking and cardiovascular diseases as follows. In summary for the purposes of preventive medicine, it can be concluded that smoking is causally related to coronary heart disease for both men and women in the United States. Unfortunately, the text of the report fails to validate the conclusion.

The main thrust of the 1979 Report is with the

Editorial

Smoking and coronary heart disease: what are we to believe?

Carl C. Seltzer, Ph.D.

Cambridge, Mass.

Two recent events have raised serious questions as to what we are to believe about the conventional view that cigarette smoking is a cause of coronary heart disease (CHD).

Interpretation of ex-smoker data

The first event relates to the interpretation of ex-smoker data indicating that CHD mortality rates of persons who stopped smoking are substantially lower than those of persons who continued smoking. The interpretation given to these data is that smoking cessation directly results in the reduction of risk of heart disease mortality. The most commonly cited investigations in support of this line of thinking are the observational studies of Doll and Hill's British doctors, Hammond's American men and women, Kahn's U.S. veterans, and the Framingham Study. Underlying this alleged CHD benefit, however, is the assumption that ex-smokers are a representative sample of smokers, except in so far as they have stopped smoking. But the proof of the validity of this assumption has not been forthcoming. This is a crucial point in the comparison of the CHD outcomes in the two smoking groups. For if the assumption of representativeness is invalid and significant baseline differences are observed between ex-smokers and smokers for relevant factors, then the possibility

exists that the mortality comparison of ex-smokers and continuing smokers is biased.

For the first time in a very large series of subjects according to race and sex, we observed the proper baseline for the determination of whether or not ex-smokers were a representative sample of smokers. This baseline involved the study of the CHD-related characteristics of ex-smokers *before they stopped smoking* and their comparison with those of persistent smokers. The results of this study are briefly reviewed below.

Using the longitudinal records from the Kaiser Permanente multiphasic health check-ups, the study compared 25 CHD-related characteristics of ex-smokers *before they stopped smoking* with those of persistent smokers and nonsmokers. A total of more than 25,000 subjects, white men and women, black men and women, with three or more consecutive health check-ups formed the basis of the analysis. For the criteria of the classification of the subjects, the designated in-depth examination, and the list of CHD-related characteristics, the reader is referred to the publication.¹ The minimum of three or more examinations was used in order to insure a rigorous classification of the smoking categories. Thus, ex-smokers (persistent quitters) were subjects who had at least one examination at which they reported both a current and past history of cigarette smoking followed by at least two examinations in which they reported complete cessation of smoking. The CHD-related characteristics fell into arbitrary categories: cardiovascular manifestations (blood pressure, hypertension,

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Thus after many years of search and experimentation the mechanisms by which smoking (cigarette smoke) might enhance various manifestations of CHD have not been satisfactorily established. Many hypotheses have been advanced as explanations of possible pathways between smoking and enhancement of CHD but these remain postulations. To arrive at a conclusion that smoking is causally related to CHD proven mechanisms are the essential links between the evidence of statistical association of smokers with excess CHD in a number of countries. These proven mechanisms have not been forthcoming.

There are a number of other aspects of smoking and CHD in the 1979 Report which are not supportive of the causal hypothesis. For example, angina pectoris, an important manifestation of CHD, is not deemed to be at risk from smoking. In this connection the 1979 Report states:

the predictive risk factor association of smoking with the incidence of angina pectoris is not clear and epidemiological data on the association between cigarette smoking and angina pectoris and cerebrovascular disease manifested as stroke are not conclusive.

In discussing the effect of smoking on blood lipids the 1979 Report finds that: "The data are not very uniform. As for cholesterol its association with smoking is minimized stating that:

There may indeed be a minor tendency for cigarette smokers to have slightly elevated blood cholesterol levels for whatever reasons. And in discussing cholesterol levels in the Framingham Study it is concluded that: "These differences were too small to account for the observed difference in risk associated with type of smoking habit. Also with regard to the Tromsø and Framingham studies the 1979 Report asserts that: "almost identical HDL cholesterol levels among smokers and non smokers were found there was no significant association between them."

The 1979 Report also discusses the effect of smoking on the vascular system in proper context. It states: "The transient effect of smoking on the heart rate and blood pressure is well known. The relationship between smoking and hypertension is made crystal clear in the following quotations. Available data indicate that smoking is not a major

risk factor for hypertension and in practice the association is slightly negative - Cigarette smoking does not induce chronic hypertension - There is no apparent relationship between smoking and incidence of hypertension."

The 1979 Report is also notable for what it does not mention or fails to give adequate attention to. No mention is made that there is an absence of excess CHD risk in the elderly (ages 65 and over) in the continuation of cigarette smoking.¹ No mention is made that the evidence of an association between CHD and duration of cigarette smoking is not clear owing to the absence of such an association in the Framingham Study, the Albany Heart Study, Dorn's U.S. veterans study, and the Canadian veterans study.² No mention is made of the importance of other variables known to be important in CHD (in their confounding effects) such as educational level, income class, marital status, occupation, job advancement and ethnicity.³ The 1979 Report concludes that cigarette smoking is causally related in United States women but fails to mention that the Framingham Study (the U.S. Public Health Service's own study) found essentially no relation between cigarette smoking and heart disease in women.⁴ "The constitutional hypothesis is dogmatically dismissed principally on the basis that "risk of smokers reverts to normal or nonsmokers level after they cease to smoke necessitating a change in ex smokers in their constitutional factor in midlife. Such a view shows a disturbing lack of understanding of the constitutional hypothesis and is contrary to the evidence that ex smoker CHD rates are related to their basic characteristics rather than to a flat out ascription to smoking cessation. The evidence of a constitutional genetic factor from the data of twin studies is stated to be inconclusive despite the consistent results of Cederlof and colleagues,⁵ Friberg and associates,⁶ Lundman,⁷ Liljefors,⁸ and De Faire.⁹ No mention is made of Burch's contention that the secular trends in sex specific and age specific death rates from CHD in England and Wales (1921-1973) strongly support the constitutional hypothesis."¹⁰

Apart from the matter of association perhaps the most common argument raised in behalf of the causal hypothesis is that stopping smoking reduces the risk of CHD. This has been considered by the American Heart Association's 1977 Ad Hoc

statistical association of cigarette smoking and CHD. The association showing smokers relative to nonsmokers having more specific manifestations of CHD in the form of myocardial infarction and sudden death is evident. So is the association of smokers with necropsy manifestations of atherosclerosis. These conditions have strong appeal to epidemiologists and others to draw causal conclusions as to the effect of smoking on CHD despite the universal dictum stated by the 1979 Report that 'correlation is not synonymous with causation'. Beyond the matter of statistical association of smokers with myocardial infarction, sudden death and atherosclerosis (from necropsy), the necessary evidence of a causal connection is not clear nor determined. The cold reality is that the mechanisms by which smoking (tobacco smoke) allegedly enhances CHD have not been established. As far back as 1964 the Surgeon General's Advisory Committee on Smoking and Health found no unique cardiovascular effects were demonstrated to seem likely to account for the observed associations of cigarette smoking [smokers] with an increased incidence of coronary disease. Since then however many hypothetical mechanisms have been advanced starting with the Surgeon General's 1967 Report¹ successively to the latest 1979 Report. Facile postulations have been the order of the day with nicotine and carbon monoxide featuring among the guilty culprits.

At times the 1979 Report is quite candid as to what is known concerning the mechanisms by which cigarette smoke affects various aspects of CHD. With regard to atherogenesis the 1979 Report states: 'At the present time animal experiments on atherogenesis and CO have provided conflicting data and must be regarded as unsatisfactory. Further, the mechanisms by which smoking enhances atherogenesis require elucidation. And still further, specific morphological features of plaques that would be characteristic of smoking have not been delineated. And again:

The overall impression from available data is that nicotine does not affect atherogenesis in animals. The summary on this subject seems very weak. First it remarks there is no reasonable doubt that cigarette smoking enhances atherogenesis, while further on in the same summary section it confesses that 'Relatively little is known about the mechanisms by which smoking enhances atherogenesis or in-

creases the risk of heart attack. The 1979 Report is singularly maladroit in summarizing this area of concern.

In connection with myocardial infarction the 1979 Report states: 'The mechanism of effect is usually attributed to an enhancement of coronary atherosclerosis in smokers and the consequent occurrence of cardiac ischemia and ischemic necrosis of heart muscle. Myocardial infarction then is attributed to the smoking enhancement of atherosclerosis which at present is based on speculation or doctrinal statements rather than on rigorously interpreted evidence. Note the following quotations: it can be *hypothesized* (my italics) that patients on the border of myocardial ischemia may be pushed into impending or actual infarction by the effects of nicotine and CO and it may be *speculated* (my italics) that in the presence of coronary atherosclerosis of a degree insufficient to cause ischemia, the action of smoking on platelet pathophysiology may precipitate occlusive thrombosis and infarction. No wonder the 1979 Report finds:

A major need is to understand better the mechanisms by which smoking can induce or affect the evolution of myocardial infarction.

As for the mechanisms by which smoking may precipitate sudden cardiac death, the 1979 Report states: 'The mechanisms *postulated* (my italics) to explain the association of sudden cardiac death with smoking have been described under atherogenesis and under myocardial infarction as *possible* (my italics) mechanisms for effects of smoke, nicotine and CO. It is of collateral interest that the 1979 Report finds that 'The act of cigarette smoking does not appear to be immediately related in time to sudden death. The section on sudden death is concluded with the following:

The mechanisms by which smoking might induce sudden death in addition to an exacerbation of coronary artery atherosclerosis can be *hypothesized* (my italics) from experiments that indicate that an exacerbation of regional ischemia may promote electrical instability of the heart fibrillation or asystole. Further research will be required if these mechanisms are to be well understood and if they are to be shown to be actual mechanisms in man in relation to smoking and sudden death. Medicine will agree with the 1979 Report when it states: 'The mechanisms of sudden death, its precursor states and preventive therapy require further elucidation.

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Information for authors

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Committee on Cigarette Smoking and Cardiovascular Diseases as the final link in the chain of evidence incriminating cigarette smoking as a causal factor in cardiovascular disease. The 1979 Report asserts that Cessation of cigarette smoking reduces over time the increased risk attributable to smoking toward the risk of nonsmokers. That these views are untenable is now apparent from the new evidence we presented in the first part of this article.

Conclusions

What then remains in the 1979 Report on CHD with which we can readily agree? We can agree with the 1979 Report that coronary atherosclerosis is of primary importance in the development of CHD through myocardial ischemia. We can agree that the available necropsy data indicate that cigarette smokers tend to have more severe and extensive atherosclerosis of the coronary arteries than nonsmokers. But this does not mean *ipso facto* that cigarette smoking enhances atherosclerosis for the mechanism(s) by which smoking might enhance atherogenesis or increase the risk of heart attack have not been established. There have been no consistent clinical or experimental data in animals or man that clearly support the leap from association to enhancement.

We can also agree that there is a statistical association between cigarette smoking and CHD in the United States. While it is true as well with regard to some western European countries no significant statistical associations between smoking and CHD have been reported in Finland, the Netherlands, Italy, Greece, Yugoslavia, Japan, and Puerto Rico.¹¹ No convincing evidence has been forthcoming to account for the absence of associations in so many countries, some of which are not too far removed in their nutritional and metabolic circumstances from the U.S. This explains the structure in the summary statement in the 1979 Report limiting the conclusion to men and women in the United States.

Accordingly, the statistical associations of cigarette smokers with atherogenesis, myocardial infarction, and sudden death in a limited geographical sense are what remains from the assertion that smoking is causally related to CHD. Since as the 1979 Report points out, mere association is not synonymous with causation, this is

insufficient for valid scientific inference without attendant support from clinical and experimental data. This attendant support is lacking since the necessary mechanisms indicating how cigarette smoking might possibly enhance CHD are either unknown or not established and owing to the absence of proof that stopping smoking reduces CHD.

The associations, however, still remain to be explained. In the case of ex-smokers, we found that self-selection appeared to be responsible for the differences in CHD outcomes between ex-smokers and continuing smokers. That self-selection may also be the basis of the CHD differences between smokers and nonsmokers has not been ruled out. The crucial study of baseline characteristics of smokers and nonsmokers remains to be performed by epidemiologists. The constitutional hypothesis must be examined closely and without prejudice for possible explanations.

For the present, then, it is reasonable to believe that stopping smoking does not reduce the risk of CHD and that there is no established proof that cigarette smoking is causally related to coronary heart disease.

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Table 1 Clinical and electrocardiographic data

| Case | Sex | Sport | First observation | | Last observation | | Remarks |
|------|-----|------------|--------------------------------|-----------------------|--------------------------------|----------------------|---|
| | | | Age (yrs) | Resting ECG features | Age (yrs) | Resting ECG features | |
| 1 | M | Marathon | 22 | Wenckebach | — | — | Normalization of A V conduction after sympathetic maneuvers drugs exercise AVD after pine |
| 2 | M | Skating | 15 | Normal A V conduction | 20 | Wenckebach | Valsalva phase 4 induced Wenckebach Normalization of A V conduction after sympathetic maneuvers drugs exercise E after atropine |
| 3 | M | Walking | 24 | Wenckebach | — | — | Normalization of A V conduction after sympathetic maneuvers drugs exercise |
| 4 | M | Skating | 20 | Wenckebach | — | — | Probable dual A V nodal pathway Normalization of A V conduction after drugs and exercise Poor sinus node response to atropine |
| 5 | M | Swimming | 13 ¹ / ₄ | Wenckebach | 15 | 1 (PR 0.24 to 0.36) | Normalization of A V conduction after sympathetic maneuvers drugs exercise |
| 6 | M | Basketball | 19 | Wenckebach | 20 ¹ / ₂ | Wenckebach EAR | Normalization of A V conduction after sympathetic maneuvers and exercise Drug tests refused Disappearance of A V conduction disturbances after training |
| 7 | M | Soccer | 27 | 1 (PR 0.28) | — | — | Wenckebach during isoproterenol administration and exercise |
| 8 | M | Tennis | 14 | Wenckebach | 16 | 1 (PR 0.18 to 0.28) | MVP AHB after EP Probable dual A V nodal pathway Normalization of A V conduction after sympathetic maneuvers drugs exercise AVD after atropine |
| 9 | M | Basketball | 18 | 1 (PR 0.28) | 23 ¹ / ₄ | Wenckebach | MVP Normalization of A V conduction after sympathetic maneuvers drugs exercise |
| 10 | M | Cycling | 10 | Wenckebach, VPB | 21 | Wenckebach VPB | MVP Normalization of A V conduction after sympathetic maneuvers drugs exercise AVD after atropine Exercise abolished VPB |

Abbreviations: 1 = first degree A V block; AHB = advanced heart block; AVD = atrioventricular dissociation; EAR = ectopic atrial rhythm; EP = electrophysiology; MVP = mitral valve prolapse; VPB = ventricular premature beats; Wenckebach = second-degree A V block, Wenckebach type (Mobitz I).

was documented in the youngest athlete (Case 5) at the age of 13¹/₄ years after 4 years of competitive activity and in the oldest one (Case 7) at the age of 27 years after he had practiced his sport for 9 years.

Previous ECGs of Cases 5, 6, 8, 9 and 10) were available. The data from a maximum

of 6 years (Case 10) to a minimum of 15 months (Case 6). The first ECG showed the spontaneous occurrence of Wenckebach second degree A V block in Cases 5, 6, 8 and 10, first degree A V block (PR 0.28 sec) in Case 9, and normal A V conduction in Case 2 (PR 0.16).

Subsequent ECGs evidenced remarkable variation

Wenckebach second degree A-V block in top ranking athletes: an old problem revisited

Paolo Zeppilli M.D.*
Riccardo Fencic M.D.
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Marco Maria Pirrami M.D.
Giovanni Caselli M.D.**

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Athletes ECGs represent a major problem for many cardiologists and sports physicians as in some cases the tracings significantly differ from those of normal untrained persons and sometimes closely resemble pathological ECG patterns like ventricular hypertrophy^{1,2} and ST-T wave ischemic changes.^{3,4} These findings have been attributed to the anatomical and physiological cardiac adaptations to heavy prolonged training mainly of the endurance type.⁵ Particularly sinus bradycardia, bradyarrhythmias and first degree A-V block have been attributed to the absolute or relative increase of resting vagal tone following training and therefore these have been regarded as physiological phenomena.

Wenckebach second degree A-V block is a very uncommon finding in normal people but is significantly more frequent in young athletes, physically active middle aged persons and is surprisingly frequent in horses.

Notwithstanding these epidemiological data have not solved the central question if a vagogenic mechanism by itself can be entirely responsible for these anomalies. The nightly occurrence of second degree A-V block of Wenckebach type in clinically normal students seems to support the opinion that purely functional A-V

conduction disturbances may occur.⁶ On the other hand this reassuring view has been recently questioned by Young and associates⁷ as they observed in seven out of 16 adolescents and young adults the progressive worsening of A-V conduction up to fixed complete heart block.

In order to ascertain the organic or functional nature of conduction disturbances in athletes invasive electrophysiological investigations could be performed. However as the large majority of athletes who undergo cardiological examination are clinically asymptomatic and fit we believe it ethically correct to attempt only a noninvasive evaluation of conduction abnormalities in these athletes and to refer to invasive electrophysiological studies only those athletes with abnormal responses.

Since 1977 we began to submit all athletes with major A-V conduction disturbances to a noninvasive protocol study consisting of reflex autonomic tests, autonomic drug administration and physical exercise. The present paper reports the results of such a diagnostic approach performed in a group of 10 top ranking athletes with Wenckebach type (Mobitz I) second-degree A-V block.

Material and methods

Ten males 15 to 27 years old were referred to us by the Physicians of Sports Medicine Institute of Rome because of the spontaneous or induced occurrence of Wenckebach second-degree A-V block on the ECG during a routine medical evaluation for sports aptitude. They practiced different sports mostly of an endurance type (Table I). Wenckebach second degree A-V block

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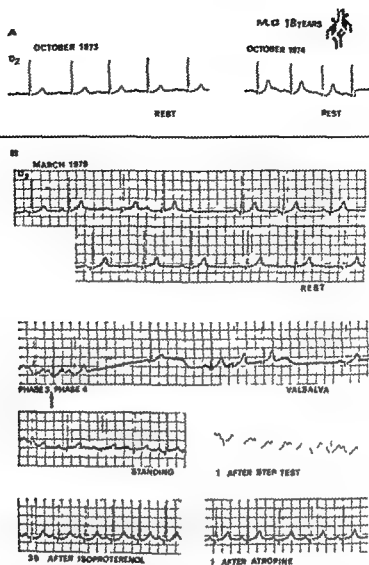


Fig 2 Case 9 Professional basketball player Mitral valve prolapse 4 First control tracing after 4 years of sports activity ECG evidences first-degree A V block (PR 0.28 sec) One year later a normal A V conduction pattern is observed B Last control tracing in March 1979 (at age 24 years) Wenckebach type A V block normalized by standing exercise isoproterenol and atropine administration Valsalva phase 4 induces sinus arrest with junctional escape beats and atrial premature beats

diograph at a paper speed of 25 mm/sec. Subsequently, all subjects were submitted to the following maneuvers:

1. Fyball pressure (FP), right (RCSP) and left carotid sinus pressure (LCSP)
2. Graded Valsalva maneuver (Valsalva) using a sphygmomanometer inflated up to 40 mm Hg for as long as possible
3. Rapid open hyperventilation (ROHV) for at least 30 seconds
4. Rapid standing test

ECG recording was continued for 10 seconds before was continued throughout the test and for 10 seconds after each test.

Basal tracings were analyzed for (1) type of rhythm and sinus rate in beats/minute (b/min) by averaging 5 P-P intervals and (2) A-V conduction pattern.

The effects of reflex tests on S-A and A-V nodes were evaluated (1) by measuring the maximum and minimum sinus rate achieved during and after each test and by checking for the possible occurrence of a shifting of the atrial pacemaker, sinus arrest, or S-A block. (2) by observing if any change in A-V conduction occurred.

Pharmacological tests First a bolus of isoproterenol 5 mcg \times 70 kg/body weight (BW) was administered intravenously under continuous

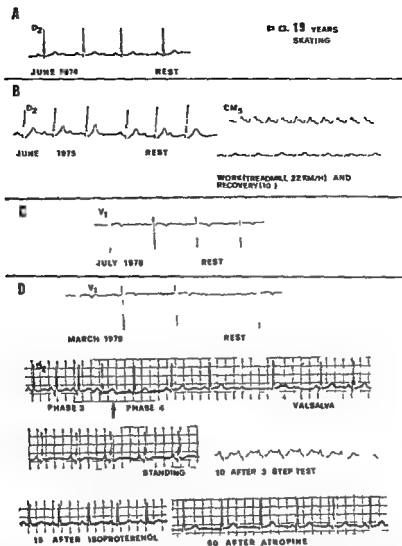


Fig. 1 Case 2 World ranking skater. A First control tracing after 3 years of sports activity normal ECG at rest. B One year later Wenckebach phenomenon at rest is observed. A V conduction is completely normalized during exercise. C Three years later Wenckebach A V block is not appreciable. D March 1979 Wenckebach A V block at rest. A V conduction is normalized by standing, exercise, isoproterenol and atropine administration. Valsalva phase 4 induces an abrupt appearance of Wenckebach second degree A V block without a significant reflex sinus bradycardia. There is transient shifting of the atrial pacemaker after atropine.

ability of A V conduction pattern (Figs 1 to 3) mainly in relation to the intensity of training but the progression to advanced or fixed complete heart block has never been documented.

All athletes at the time of our investigation were well trained and were completely asymptomatic. Family and personal histories were accurately taken. Furthermore, since athletes are frequently motivated to minimize their symptoms whenever possible, we tried to obtain the athletic history from their coaches. Physical examination, echocardiogram and phonocardiogram were taken in all subjects. Echocardi-

graphic findings diagnostic of mitral valve prolapse (MVP)^{21, 22} were present in Cases 8, 9 and 10. Cases 9 and 10 additionally had a variable mid-systolic click. Despite repeated auscultations no murmurs or clicks were found in Case 8 (silent prolapse).²³ None of these athletes had physical features characteristic of Marfan's syndrome²⁴ even if Patient No. 9 was 7 feet tall.

Reflex autonomic tests. After informed consent to protocol study had been obtained in all athletes a basal standard ECG was recorded after 15 minutes rest in the recumbent position with a multichannel Hewlett Packard electrocar-

Table II Effects on S A and A V nodes function of reflex autonomic tests drugs exercise

| Case | Control ECG | Vagal maneuvers | Valsalva | | ROHV | Stand | Isoproterenol | Atropine | Exercise |
|------|------------------------------|---------------------------------|-------------|----------------------|-------------|-------------|-------------------|----------------|------------------|
| | | | Phase 2 3 | Phase 4 | | | | | |
| 1 | SR 68† Wenckebach | 66 Wenckebach | 95 0 22‡ | 69 Wenckebach | 124 0 16 | 92 0 17 | 94 0 20 | AVD 86 0 16 | 18" 0 16 |
| 2 | SR 50 Wenckebach | 47 Wenckebach | 100 0 12 | 75 Wenckebach | 100 0 18 | 60 0 20 | 94 0 14 | 94 EAR 0 14 | 19 0 15 |
| 3 | SR 63 1 (PR 0 24 to 0 35) | 60 Wenckebach | 100 0 16 | 62 1* (PR 0 24) | 107 0 16 | 70 0 22 | 88 0 16 | 100 0 16 | 180 0 14 |
| 4 | SR 55 Wenckebach | 43 Dual A V node pathway | 79 0 24 | 58 Wenckebach | 100 0 22 | 67 0 24 | 76 0 20 | 70 0 20 | 184 0 20 |
| 5 | SR 75 1 (PR 0 24 to 0 36) | 60 1 (PR 0 36) | 88 0 16 | SA 75 1 (PR 0 20) | 115 0 14 | 75 0 20 | 96 0 16 | 96 0 15 | 18 0 14 |
| 6 | SR 60 EAR Wenckebach | 49 EAR Wenckebach | 71 0 20 | 43 Wenckebach | 88 0 22 | 50 0 20 | — — | — — | 140 0 16 |
| 7 | SR 83 1 (PR 0 28) | 80 1 (PR 0 26) | 98 0 24 | 90 1 (PR 0 26) | 120 0 22 | 100 0 22 | 100 Wenckebach | 124 0 18 | 16 Wenckebach |
| 8 | SR 60 1 (PR 0 18 to 0 28) | 58 AHB dual A V node pathway | 100 0 14 | 75 PR 0 16 | 100 0 14 | 65 0 14 | 94 0 16 | AVD 90 0 14 | 18" 0 16 |
| 9 | SR 74 Wenckebach | 67 Wenckebach | 120 0 12 | SA 45 PR 0 14 | 100 0 18 | 100 0 18 | 90 0 18 | — 0 16 | 15" 0 16 |
| 10 | SR 66 Wenckebach | 58 Wenckebach | 88 0 16 | 60 Wenckebach | 100 0 20 | 70 0 20 | — — | AVD 90 0 16 | 187 0 16 |

†Sinus rate beats/minute

‡PR interval duration-seconds.

Abbreviations 1 = first degree A V block AHB = atrioventricular heart block AVD = atrioventricular dissociation EAR = ectopic atrial rhythm MVP = mitral valve prolapse ROHV = rapid open hyper-ventilation SA = sinus arrest SR = sinus rhythm Stand. = standing up VPB = ventricular premature beats Wenckebach = second-degree A V block, Wenckebach type (Mobitz I)

In assessing an abnormal sinus node function the following experimental criteria were utilized

- 1 A sinus arrest lasting more than 3 seconds after vagal maneuvers
- 2 An inadequate sinus rate increase after physical exercise
- 3 Isoproterenol test
 - a A sinus rate increase of less than 20 b/minute

b A shifting of the atrial pacemaker or emergence of a junctional rhythm

4 Atropine test¹¹

- a A percent shortening of the basal sinus cycle length of less than 30%
- b A target rate of less than 90 b/minute
- c A heart rate increase sustained by non sinusal pacemakers

In assessing an abnormal atrioventricular node function the following criteria were utilized

Fig 4 (Case 1)

Wenckebach type I block at rest and after exercise

1 Atrial juvenile team Mitral valve prolapse First control tracing January 19 6
3 7 years later first degree A V block at rest with concertina like variation of block induced by exercise pressure Probable dual pattern of A V conduction with sinus pressure as indicated by a progressive or abrupt lengthening of the PR A V conduction C Atropine administration transient A V dissociation due to blocked by normalization of A V conduction D Normal A V conduction during

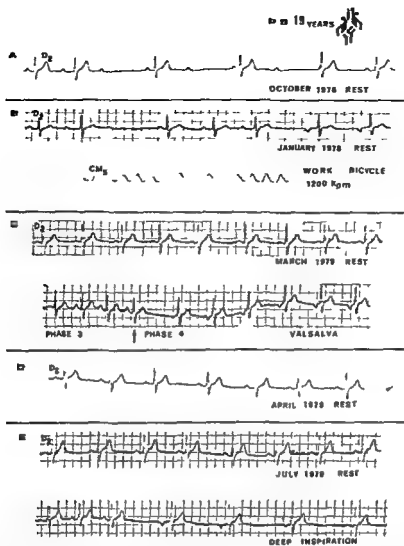


Fig 3 Case 6 Professional basketball player A First control tracing after 6 years of sports activity Wenckebach type block is evident B Fifteen months later Wenckebach A V block and spontaneous shifting of the atrial pacemaker is observed Exercise completely normalized the A V conduction C Last control tracing one month after forced detraining, because of an ankle trauma ECG at rest shows normal A V conduction (PR 0.20 sec) Shifting of the atrial pacemaker during Valsalva phase 4 is appreciable D and E two and 5 months later (still inactive) normal A V conduction Abrupt change of the atrial pacemaker is induced by deep inspiration

ECG recording until the control heart rate was resumed (usually after 5 to 10 minutes). At least 15 minutes after the isoproterenol test atropine sulphate in a single dose of 0.02 mg/kg/BW was administered intravenously within 30 seconds. The ECG was recorded continuously until a stable maximum sinus rate was achieved and then at the fifth, tenth, fifteenth and twentieth minute after the drug infusion. The isoproterenol test was not performed in Case 10 because of ventricular premature beats at rest. Subject No. 6 refused pharmacological tests.

Exercise On the following day the athletes were submitted to stress tests consisting of a 3 minute Step Test and after an adequate recovery a maximal continuous multistage exercise test on a bicycle or treadmill ergometer. The maximum and total workload sustained, the maximum heart rate and the $\dot{V}O_2$ consumption ($\dot{V}O_{2max}$) were measured. The ECG was monitored during and after effort (usually using a CM lead) for an accurate analysis of any A V conduction modification, ST and T wave changes and the occurrence of arrhythmias.

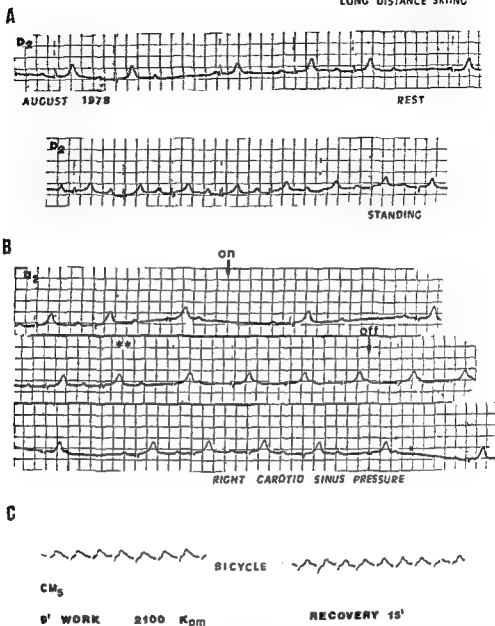


Fig 5 Case 4 Olympic ranking long distance skier A Wenckebach second degree A V block at rest with junctional escape beats Standing First degree A V block (PR 0.24 sec) is still present B Right carotid sinus pressure probable dual pattern of nodal A V conduction with evolution from Wenckebach phenomenon (of fast pathway) to 1:1 conduction with markedly prolonged PR interval (0.60 sec slow pathway) C Normal A V conduction during work

lized (1) in occurrence of A V conduction worsened during sympathetic stimulations or parasympathetic inhibition or exercise and (2) the absence of normalization of basal A V conduction disturbances during the same tests

Results (Table II)

Reflex autonomic tests Vagal maneuvers induced significant slowing of sinus rate in six

cases (Nos 2 4 5 6 9 and 10) and had minimal or no effects in the remaining four In Case 8 EP caused a high degree A V block (Fig 4)

RCSP and LCSP induced an abrupt or progressive remarkable lengthening of PR interval with maintenance of 1:1 nodal A V conduction in Cases 4 and 8 suggesting a dual pattern of nodal A V conduction (Figs 4 and 5) Sinus node response to Valsalva followed a physiological

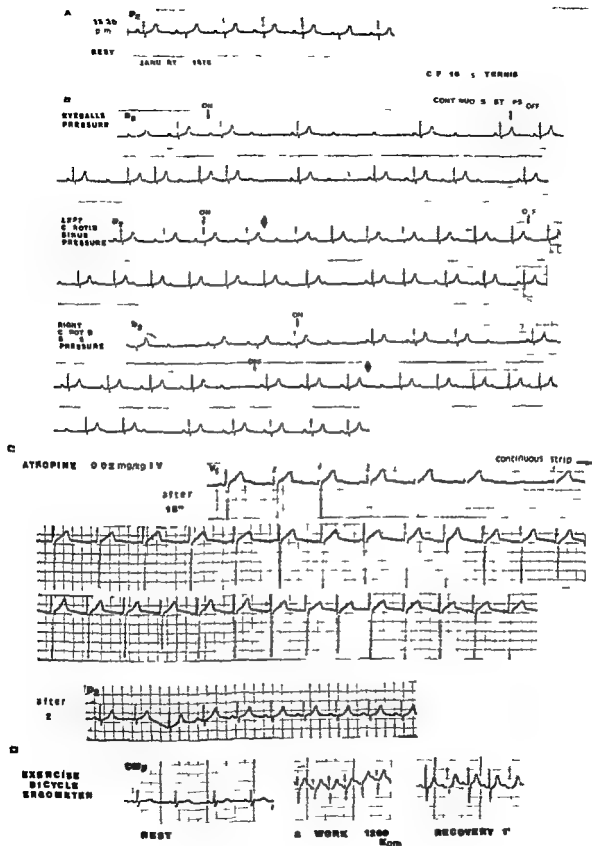


Fig 4 For legend see facing page

of sinus node to Standing was quite variable ROHV and/or Standing normalized A V conduction in eight cases (Nos 1 2 3 5 6 8 9 and 10) and improved it in Cases 4 and 7

Pharmacological tests Isoproterenol induced the expected increase of sinus rate in all cases This drug normalized A V conduction in all cases except one (Case 7 Fig 6) in which a Wenckebach A V block arose when sinus rate reached 90 b/minute In Case 4 a reduced response of sinus node to atropine was observed because of a target rate of less than 90 b/minute and a percent shortening of basal sinus cycle length inferior to 30%

Atropine induced a transient shift of the atrial pacemaker in Case 1 (Fig 1) and the occurrence of an accelerated junctional rhythm with complete or incomplete atrioventricular dissociation in Cases 1 8 and 10 (Fig 4) Sinus node response to atropine was within normal limits in the remaining five cases Atropine normalized A V conduction in all cases (Figs 1 to 6)

Exercise All athletes achieved the maximal age predicted heart rate in response to the highest workloads The physical performance of each of our athletes was adequate to his degree of training (Case 10 sustained a maximum workload of 2300 Kpm —375 Watts—on the bicycle) VO max values were over 45 ml /kg /min in all cases with a peak value of 71 ml /kg /min in Case 3

None of the subjects showed ST and T wave abnormalities and arrhythmias during effort Exercise induced the complete disappearance of ventricular premature beats even at low workloads in Case 10

Work normalized A V conduction in all subjects except one (Case 7 Fig 6) in whom a transient Wenckebach phenomenon of nodal conduction was observed at a heart rate of 125 beats/minute

Follow up studies Case 1 was seen again 11 months after the study when he was still well trained ECG at rest was unchanged and A V conduction anomalies immediately and completely disappeared after sympathetic reflex stimulations and exercise Case 6 (Fig 3) was seen again in March 1979 13 months after our study when he had been inactive for 1 month because of an ankle trauma The ECG at rest evidenced a 1:1 A V conduction at normal PR duration which was not influenced by reflex vagal stimulations

Valsalva phase 4 induced an abrupt change of the atrial pacemaker The last control examination in July 1979 after 5 months of inactivity confirmed the complete disappearance of A V conduction abnormalities and the persistence of an induced shift of the atrial pacemaker

Discussion

The introduction of intracardiac electrophysiological investigations has allowed a precise localization of sites of A V conduction disturbances and a better definition of the prognosis of different types of A V blocks " On this regard the occurrence of Wenckebach second degree A V block in apparently normal persons " and in trained athletes " has been regarded as a vagally mediated functional disturbance of impulse conduction localized to the A V node and considered a benign clinical event

Unfortunately this optimistic view has been recently questioned by Young and associates " who found the possible evolution of Wenckebach type second degree A V block to advanced or complete block in adolescents without clinical findings of cardiac disease Those authors also pointed out that neither a positive response to exercise and atropine nor the results of the electrophysiological investigations can be considered reliable prognostic indexes However Hanne-Paparo and co workers " described a case of a 30 year old sportsman with Wenckebach A V block who had been followed for 10 years without evidence of progressive deterioration of A V conduction

More recently Murayama and associates " showed that ECG changes observed in 102 Japanese olympic ranking athletes (Tokio Olympic Games 1964) during the competitive period (including first and second degree A V block) completely disappeared in 95% of subjects within 4 years from the end of physical activity

Our study seems to be in full agreement with the observations of Hanne-Paparo and colleagues and Murayama and associates for the following reasons

- 1 The favorable follow up studies of six of our athletes

- 2 The characteristic spontaneous variability of A V conduction pattern in relation to the intensity of training or forced detraining (Figs 1 2 and 3)

MAY 1979

D V 27 YEARS

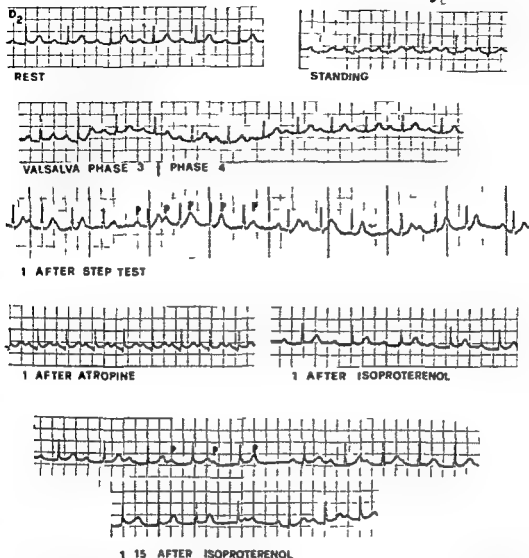


Fig 6 Case 7 Professional soccer player First-degree AV block at rest Worsening of AV conduction up to Wenckebach second-degree AV block after Step Test and isoproterenol administration After atropine 1:1 AV conduction with a PR interval of 0.18 sec is observed

behavior²⁷ in Cases 6 and 10 Valsalva phase 4 induced a sinus arrest of 1.8 seconds followed by junctional escape beats and premature atrial beats in Case 9 (Fig 2) in Case 5 a short period of sinus arrest interrupted by a single junctional escape beat and followed by regular sinus rhythm was observed The remaining six cases (Nos 1 2 3 4 7 and 8) did not show any slowing of sinus rate during Valsalva phase 4 (Figs 1 and 6) Valsalva phase 4 induced a Wenckebach type

second degree AV block in Cases 1 and 2 (Fig 1)

Valsalva phase 2 and 3 completely normalized AV conduction in seven cases (Nos. 2 3 5 6 8 9 and 10) (Fig 1 to 3) in Cases 1 and 4 (Fig 5) it improved Wenckebach second degree block to first degree block while it caused only a small shortening of PR interval duration in Case 7 (Fig 6) An adequate increase of sinus rate during ROHV was observed in all subjects The response

block does not seem indicated provided that

- 1 They are asymptomatic
- 2 A complete noninvasive cardiological examination shows the absence of any cardiac pathological involvement
- 3 An immediate normalization of A V conduction pattern can be obtained with reflex sympathetic stimulations, sympathomimetic or vagolytic drugs and physical exercise

Wenckebach second degree A V block in asymptomatic athletes with MVP features probably does not affect the prognosis if normal responses to the aforesaid provocative tests are observed

Summary

The occurrence of Wenckebach second degree (Mobitz I) A V block in apparently normal persons still provides a puzzle for the cardiologist as the benign nature of this event has been recently questioned. This problem becomes more intriguing when Wenckebach A V block is encountered in asymptomatic top ranking athletes, because of medico legal implications. We report 10 cases of highly trained athletes including three with mitral valve prolapse (MVP) features with a spontaneous or induced Wenckebach second degree A V block.

Previous ECGs of six subjects dating from a maximum of 6 years to a minimum of 18 months were available. Deterioration of A V conduction has never been documented and all six cases have remained asymptomatic for the whole follow up period.

Athletes have been submitted to a protocol study consisting of ECG recording at rest during and after vagal and sympathetic reflex maneuvers, drug administration (isoproterenol and atropine), submaximal and maximal exercise.

Nine subjects have been considered to have normal responses of the A V node to provocative tests since conduction disturbances were improved or normalized by reflex sympathetic stimulations and were completely normalized by autonomic drug administration and exercise.

One athlete showed abnormal responses to tests. In order to give a conclusive prognostic and medico legal assessment we advised him to submit to a complete electrophysiological investigation.

Wenckebach second degree A V block in athletes

may be a more common finding than so far described, especially when a systematic search is made. In our opinion this event can still be considered a vagally induced benign feature of athletes' heart provided that an immediate improvement of A V conduction is obtained in response to reflex sympathetic maneuvers and that a complete normalization after sympathomimetic and vagolytic drug administration and physical exercise is observed.

The clinical histories of our athletes and the observed complete disappearance of conduction disturbances after detraining strongly support this opinion.

Wenckebach second degree A V block in asymptomatic athletes with MVP features probably does not affect the prognosis if similar favorable responses to the aforesaid tests are observed.

We are grateful to Dr. Antonio Greco for providing facilities and continuous encouragement in our studies. We also thank Prof. Antonio Venerando for his scientific assistance in processing the manuscript and Mr. G. Madeddu for his secretarial assistance. We are additionally indebted to Dr. Sima Sandric, Dr. Fernando Cecchetti and Dr. Antonio Spataro for their help in evaluating the athletes.

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3 The significant improvement of A V conduction obtained even after simple sympathetic maneuvers and the complete normalization induced by autonomic drug administration and exercise in all athletes except one

Nevertheless abnormal responses of A V nodal conduction to isoproterenol and exercise were appreciable in Case 7 (Fig 6) In order to obtain a conclusive prognostic and medico legal assessment we advised this athlete to submit to an invasive electrophysiological investigation which up to now he has refused

Functional vagogenic depression of A V nodal conduction in athletes seems therefore confirmed by our observations However a hyporeactivity of sinus node to vagal maneuvers as evidenced by the lack of significant reflex sinus bradycardia during Valsalva phase 4 and abnormal responses of sinus node to atropine administration have been observed in five cases (Nos 1, 2, 4, 8 and 10, Figs 1 and 4) These events could suggest the possibility of sinus node dysfunction or sick sinus syndrome (SSS)^{2, 34}

Nevertheless similar behavior after atropine administration has been reported in apparently normal persons of different ages especially in young subjects and when low doses of the drug were employed¹ The effects of different doses of atropine on S A and A V nodes have been recently investigated by Das and colleagues S A node response was characteristically bimodal as sinus rate slowed at smaller doses and accelerated at higher doses while A V node showed acceleration of conduction whatever the dose of atropine administered

The above mentioned authors suggested that like any other receptor blocking agent¹ atropine can produce a transient stimulating effect namely a vagomimetic response Therefore the simultaneous occurrence of sinus bradycardia and A V conduction facilitation could be explained by the different electrophysiological effects of acetylcholine on the rates of impulse formation and impulse conduction Moreover the appropriate sinus rate increase after isoproterenol infusion^{1, 2} and exercise³ seems to confirm the normality of sinus node automaticity in our athletes Therefore despite the recent report of Roland and associates³⁵ we strongly doubt that at present our athletes could be affected by SSS On the other hand in spite of our

apparently reassuring opinion long term follow up studies are mandatory in order to verify the possible role of heavy prolonged training in the pathogenesis of SSS at a later time in life

It now remains to explain why

1 A training mediated increase of vagal tone has induced in our athletes major A V conduction disturbances instead of sinus bradycardia which is the usual autonomic response of the heart to training^{3, 36} and

2 The hyporeactivity of the sinus node to Valsalva and atropine administration exists in some of our athletes

As our subjects did not show any evidence of chronic degenerative diseases involving the autonomic nervous system^{1, 30} a possible alternative explanation of the aforesaid findings could be found in an individually different distribution of the parasympathetic influence on S A and A V nodes in otherwise normal persons

Wenckebach second degree A V block and mitral valve prolapse in athletes MVP may be an unexpected finding in asymptomatic top ranking athletes^{4, 7, 31, 3} In accordance with the findings of Barlow^{32, 3} we previously suggested that in the assessment of the sports aptitude of athletes with MVP features a permissive criterium has to be adopted³ provided that no ventricular tachyarrhythmias at rest^{33, 3} and during effort³ have been observed However remarkable sinus bradycardia with syncope episodes³ and atrioventricular and intraventricular conduction disturbances³⁴ have been recently reported in subjects with MVP but their pathogenetic clinical and prognostic implications are still questionable

In the present report the S A and A V nodes responses to provocative tests and the follow up studies of athletes with MVP did not differ from the results in normal athletes

Therefore in our opinion the occurrence of A V conduction disturbances in asymptomatic athletes with MVP features has to be regarded in the same manner as in normal sportsmen provided that these anomalies have shown normal responses to the aforesaid protocol study

Conclusions

Our observations support the opinion that a systematic aggressive diagnostic approach in athletes with Wenckebach second degree A V

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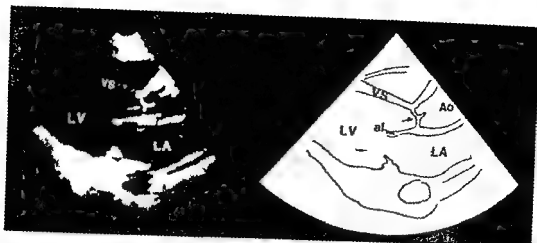


Fig 1 A left ventricular longitudinal cross sectional echocardiogram from a normal control depicting the left ventricle (LV) left atrium (LA) ventricular septum (VS) and the anterior leaflet of the mitral valve (al) The white arrow's head lies at the mouth of the aorta at the level of the aortic ring and points to the coaptation point (at mid aortic level) of the right and posterior aortic valve cusps in diastole The cusps lie well above the aortic ring

phases of the cardiac cycle were noted. The coaptation point of the aortic cusps were analyzed for its degree of echo reflection and for its location and the presence of any diastolic motion. M mode echocardiograms were analyzed for aortic root size, location of the coaptation line in diastole, echo reflectivity of the aortic cusps, and for fluttering of the mitral and aortic valve leaflets.

Study population A total of 112 consecutive patients with cross sectional echocardiographic criteria for mitral valve prolapse as previously described¹³ were analyzed for morphological appearance and mobility of the aortic valve. The longitudinal left ventricular cross sectional echocardiographic study was considered adequate for imaging the aortic valve only when two cusps were clearly seen and their motion and coaptation point could be visualized throughout diastole. This demanded that the surrounding landmarks (the interventricular septum, anterior mitral valve leaflet, and aortic root) were well visualized. M mode echocardiographic aortic root enlargement was considered present if the aortic root exceeded previously defined normal limits. Cusp thickness was considered increased when one or both cusps reflected increased echoes from any part of the cusp compared to controls and from a target of known thickness in the same patient. Downward displacement of the cusp tissue or coaptation point was assessed in real time and displacement was felt to be present when leaflet tissue or the coaptation point were

imaged inferior to the aortic valve ring toward the left ventricular outflow tract. Tricuspid valve prolapse was defined using previously described cross sectional echocardiographic criteria¹⁴ utilizing both the right ventricular longitudinal inflow tract and apical views. Seventy of mitral valve prolapse was determined using both longitudinal and four chamber apical views with severe mitral valve prolapse being present when the mitral leaflets moved well beyond the mitral ring level towards the left ventricular apex. Mild prolapse was defined as minimal leaflet displacement beyond the mitral valve ring and moderate was defined as being between mild and severe.

All studies were analyzed blindly by three echocardiographers on two different occasions. The inter- and intraobserver variability was less than 5%.

Results

Control population M mode echocardiographic aortic root measurement in 14 controls revealed a normal aortic root size in all (mean 3.3 ± 0.3 cm [SD], range 2.8 to 3.8 cm). All subjects demonstrated the coaptation line of the two visualized aortic cusps in the center of the aortic root. The two cusps appeared symmetrical with only a minimum of echo reflectivity which established the normal degree of echo reflection. Mitral valve fluttering (anterior leaflet) suggestive of aortic regurgitation was not seen in any of the control subjects and none of the 14 had any evidence of

Cross-sectional echocardiographic detection of aortic valve prolapse

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The identification of aortic valve prolapse has been limited to surgical and pathological studies.^{1,2} Read and Thal¹ in 1965 identified at surgery the coexistence of aortic valve prolapse in patients with mitral and tricuspid valve prolapse. The mucoid degeneration in the aortic valve appeared to be due to a diffuse connective tissue disorder involving the cardiac fibrous skeleton unrelated to aging. M mode echocardiography³ has been able to document mitral and tricuspid valve prolapse in part because of the larger atrioventricular annular and leaflet size rendering easy identification of the prolapsing motion. Conversely the aortic annulus is smaller and aortic cusps less voluminous and less echo reflective and thus previous noninvasive identification of aortic valve prolapse has not specifically been defined. Chandraratna and colleagues⁴ reported a single case of aortic valve prolapse demonstrated at surgery in which the M mode echocardiography revealed diastolic aortic leaflet fluttering. Rippe and co-workers⁵ reported four patients who had marked aortic valve excursions on M mode echocardiography and were thought therefore to have aortic valve prolapse. These patients

clinically did have aortic regurgitation and mitral valve prolapse and thus aortic valve prolapse syndrome was suggested. Cross sectional echocardiography provides real time evaluation of the aortic valve and thus this study was conducted to determine the prevalence and characteristics of aortic valve prolapse as defined by this noninvasive technique.

Material and methods

All cross sectional echocardiographic studies were obtained using a wide angle 84 degrees commercially available phased array system (Varian V 3000) with a transducer containing 32 mounted piezoelectric crystals with a diameter of 1.3×1.2 inches at the skin level. All studies were recorded on videotape (Sanyo) and were later reviewed in real time slow motion and frame by frame analysis. Individual frame selections for figures were photographed using a Polaroid camera. The quality of these still frame images was significantly degraded since only one half of the line density was present during the still framing. M mode echocardiographic studies were obtained using a Smith Kline Echoline 20A with a 2.25 MHz transducer. Left ventricular longitudinal and short axis views of the aortic valve were obtained using the conventional approach.⁶

Control population Fourteen subjects (mean age 51 ± 10 years [SD]) with normal cardiac catheterization and cineangiographic findings were selected to define normal aortic valve morphology and motion characteristics by cross sectional echocardiography. The thickness of the aortic cusps and their mobility during various

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Table 1 Comparison of 60 patients with mitral valve prolapse (MVP) alone with 17 cases of both MVP and aortic valve prolapse (AVP)

| N | MVP (60) | AVP (+ MVP) (17) |
|--|--------------|---------------------|
| Mean age (\pm SD) in years | 38 \pm 18 | 36 \pm 21 |
| Mean aortic root systolic size (in cm \pm SD) by M mode echocardiography | 31 \pm 0.3 | 35 \pm 0.5 |
| Aortic root enlargement by M mode echocardiography | 0 | 11 |
| Clinical aortic regurgitation | 0 | 4 |
| Tricuspid valve prolapse by cross-sectional echocardiography | 31 | 16 |
| Increased aortic cusp thick- ness by cross-sectional echocardiography | 0 | 16 |

$p < 0.01$

mean age of 36 ± 21 (SD) years (11 were female) and revealed a different aortic valve morphology and motion characteristic compared to controls

Cross sectional echocardiographic findings In 16 of 17 patients the echo reflectivity from the aortic valve cusp tissue was considered increased compared to controls. The coaptation point of the aortic valve was considered eccentric by cross sectional echocardiographic analysis in six patients while the other 11 patients showed a central positioned coaptation point. The six patients with eccentric coaptation all had three aortic valve cusps demonstrated on short axis tomographic view. The eccentricity was noted to be anterior in four (Fig 2A) and posterior in two patients (Fig 2B). Real time motion assessment revealed that unlike the controls there was downward displacement of both aortic cusps during diastole in 13 of the 17 patients whereas two cases had isolated right or posterior cusp

Sixteen of 17 patients with aortic valve prolapse demonstrated evidence of tricuspid valve prolapse on the right ventricular longitudinal inflow tract and/or apical four chamber view. The other case demonstrated a normal tricuspid valve but only an apical view was available. In 31 (52%) of the 60 subjects with mitral valve prolapse but without aortic valve prolapse tricuspid valve prolapse was demonstrated ($p = \text{NS}$). Longitudinal left ventricular and apical views were used to assess the severity of mitral valve prolapse. The severity of mitral valve prolapse in the

17 patients with aortic valve prolapse (six mild five moderate six severe) was not statistically different from that seen in the 60 cases with mitral valve prolapse without aortic valve prolapse

M mode echocardiographic and clinical findings There was no aortic root enlargement visualized by M mode echocardiography in any of the 60 patients with mitral valve prolapse without aortic valve prolapse. Mean aortic root diameter was 31 ± 0.3 cm (SD). Aortic root size was enlarged in six of 17 patients with aortic valve prolapse. The mean for all 17 patients was 35 ± 0.5 cm (SD). Evidence of anterior mitral leaflet fluttering compatible with aortic regurgitation was seen in four of 17 and in three of the four physical examination revealed a diastolic murmur compatible with aortic insufficiency. One patient had moderate aortic regurgitation by aortic root angiography with three aortic valve cusps. Three of these four patients had evidence of aortic root enlargement on M mode echocardiography whereas three of 13 without aortic regurgitation showed aortic root dilatation. Two of these four patients had diastolic aortic valve separation and fluttering as previously described.¹⁰ Two of the 17 patients had abnormal diastolic echoes from the prolapsed aortic valve protruding into the left ventricular outflow tract similar to that described by El Shahawy and co workers.¹⁴ Table I contrasts those patients with and without aortic valve prolapse.

Discussion

This cross sectional echocardiographic study has suggested the presence of aortic valve prolapse in 17 (22%) of 77 patients with mitral valve prolapse. Aortic valve morphology and motion characteristics were clearly altered in these 17 patients compared to a control population of normal subjects and to 60 patients (78%) of the group selected with mitral valve prolapse. Unfortunately the striking real time echocardiographic findings noted in these patients cannot be reproduced on still photographs as used in the representative Figs 1 and 2. The 17 patients with aortic valve prolapse showed higher degrees of aortic valve thickening, eccentricity of aortic cusps and a higher prevalence of clinical aortic regurgitation and M mode echocardiographic aortic root dilatation.

Carter and co workers¹ have classified aortic

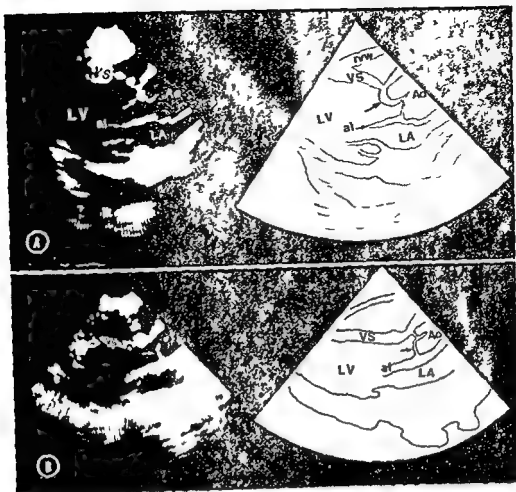


Fig 2 A A left ventricular longitudinal cross sectional echocardiogram from a patient with aortic valve prolapse demonstrating the left ventricle (LV) aorta (Ao) left atrium (LA) anterior mitral valve leaflet (al) and the right ventricular wall (rvw). The head of the white arrow lies well into the left ventricular outflow tract at mid mitral valve level and points to a marked prolapse and asymmetry of the right aortic valve cusp. B A left ventricular longitudinal cross sectional echocardiogram from a patient with aortic valve prolapse demonstrating the left ventricle (LV) left atrium (LA) aorta (Ao) and the anterior mitral valve leaflet (al). The white arrow points to a prolapsed thickened and asymmetric large posterior aortic valve cusp.

mitral valve prolapse. Cross-sectional echocardiographic evaluation revealed a central coaptation point of the two aortic cusps and relatively faint echo reflection as viewed from the left ventricular longitudinal section. Real time analysis of the aortic valve closure pattern in diastole with subsequent frame by frame analysis revealed that the coaptation point of the two cusps remained fixed throughout diastole and that there was no downward displacement towards the left ventricle during diastole. The aortic cusps were slightly convex towards the center of the aorta at the level of their coaptation point. Fig 1 demonstrates a typical example of a normal aortic valve closure pattern during diastole.

Still photos demonstrated in this manuscript

are limited to show the striking real time echocardiographic findings. Since the aortic valve cusps tended to be relatively poor echo reflectors and therefore their position was difficult to demonstrate when only one half of the line density was present on stop frame images.

Study population. The aortic valve was adequately visualized for analysis in 77 of 112 (68%) patients with cross sectional echocardiographic evidence of mitral valve prolapse. Sixty (78%) of these 77 patients had a mean age of 38 ± 18 years (SD) and in all 60 the aortic valve characteristics and motion features were identical to those of the 14 controls. These patients were considered to have mitral valve prolapse without aortic valve prolapse. The remaining 17 patients (22%) had a

changes in patients with aortic valve prolapse is present.¹⁷ Previously reported surgical experience¹⁷ suggests that a subgroup of cases exists with aortic mitral and tricuspid valve prolapse in which valvular regurgitation may require prosthetic valvular replacement.

The inability of M mode echocardiography to visualize and detect superior/inferior prolapsing motion of aortic valve produces serious limitation for this technique in the detection of aortic valve prolapse. However few features on M mode echocardiographic tracings may suggest the presence of aortic valve prolapse. The presence of increased aortic valve reflections, eccentricity of the diastolic closure line, aortic root enlargement, abnormal diastolic echoes in the left ventricular outflow tract, and the presence of fluttering of the anterior mitral leaflet can all be used to suggest the possibility of coexistence of aortic valve prolapse in patients with mitral valve prolapse.

The limitations of this cross sectional echocardiographic study are clear. First, the true prevalence of adequate visualization of the aortic valve cannot be assessed from this study since it was performed in a retrospective manner in selected patients with mitral valve prolapse referred to our echocardiographic laboratory, and thus may not be applicable to population studies in patients without mitral valve prolapse. Second, the analysis of a study population of mitral valve prolapse for the detection of aortic valve prolapse may create bias as to the actual spectrum of aortic valve prolapse. The possibility of the presence of aortic valve prolapse without mitral valve prolapse cannot be excluded from this study. In addition, we have no data comparing the actual clinical manifestations and natural history of patients with aortic valve prolapse compared to those patients with mitral valve prolapse without aortic valve prolapse. Nevertheless, this study demonstrates the potential of cross sectional echocardiography to diagnose a subgroup of patients with mitral valve prolapse with specific aortic valvular abnormalities suggesting the coexistence of aortic valve prolapse. The potential of evaluating the prevalence of aortic valve prolapse in a population with aortic insufficiency has not yet been explored.

Summary

To determine the potential for cross sectional echocardiography to define aortic valve prolapse

14 controls with a mean age of 51 ± 10 years (SD) with normal cardiac catheterization were studied by cross sectional echocardiographic left ventricular longitudinal and short axis views to define normal aortic valve morphology and motion characteristics. Similarly, 112 patients with cross sectional echocardiographic mitral valve prolapse were analyzed to determine aortic valve morphology and motion characteristics. In all 14 controls the left ventricular longitudinal view revealed the aortic valve as a faint echo reflector with symmetrical cusps whose closure point as well as the cusp tissue itself did not display any downward (or prolapsing) motion toward the left ventricular outflow tract. In the group of 112 patients with mitral valve prolapse, the aortic valve was successfully imaged for detailed analysis in 77. Sixty of these 77 (78%) had a mean age of 38 ± 18 years (SD) and revealed aortic valve morphology motion characteristics similar to controls. All of the remaining 17 patients (mean age 36 ± 21 years, 11 female) revealed a downward displacement (or prolapse) of the aortic valve during diastole. There was an increased echo reflection from the cusp tissue in 16 of 17 and in six of 17 cusp size was asymmetric producing eccentricity of the coaptation point. All six of these had three aortic cusps seen on the short axis view. The aortic root size was normal in all controls in the 60 patients with mitral valve prolapse without aortic valve prolapse whereas six of 17 patients with aortic valve prolapse had aortic root enlargement. When comparing the group with ($N = 11$) and without ($N = 60$) aortic valve prolapse the tricuspid valve was prolapsed in 16 of 17 compared to 31 of 60 ($p = NS$) and aortic insufficiency was present in four of 17 compared to none of 60 ($p \leq 0.01$).

In conclusion, cross sectional echocardiography can identify a subset of patients with mitral valve prolapse who have aortic valve prolapse in which aortic root dilatation and aortic regurgitation may be encountered. Such patients may reflect a more diffuse myxomatous degeneration of the cardiac skeleton.

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valvular prolapse into etiologies associated with intact cusps ruptured cusps loss of commissural support and ventricular septal defect with displacement of the aortic root. The patients in our study all had intact cusps as defined by echocardiography since none had evidence of serious cardiovascular disease such as dissecting aortic aneurysm ventricular septal defect or traumatic or infected aortic valve or aorta. Causes of intact cusps with aortic valve prolapse include (1) intrinsic weakness due to floppy valve syndrome with or without dilatation of the aorta (2) fraying of a cusp¹ characterized by thinning without through and through laceration which may result in the affected cusp ballooning in an aneurysm like fashion towards the ventricle and (3) excessive aortic valve tissue in patients with a congenital bicuspid aortic valve.²

Pathologic and surgical evidence of aortic valve prolapse due to floppy valve syndrome has been suggested.^{1,3,4} Read and colleagues¹ in 1965 reported the existence on histology of myxomatous transformation of the cardiac valves in surgical patients and suggested the term floppy valve syndrome. These patients they suggested may represent a possible forme fruste of Marfan's syndrome. No specific etiologic basis was identified. Seven cases of aortic valve prolapse were defined surgically by Frable² and McKay and Yacoub³ reported that 9% of 560 patients who underwent mitral or aortic valve replacement had myxomatous degeneration of the mitral and/or aortic valve. Eleven had isolated aortic valve prolapse and nine of these were men.

Previous echocardiographic studies⁵⁻⁸ to define aortic valve prolapse have been limited to M mode technique and none could be considered diagnostic or specific for aortic valve prolapse. Real time visualization of the aortic valve using cross sectional echocardiography in which a superior direction of the aortic valve can be analyzed is required to establish this diagnosis noninvasively. Due to the relatively small aortic ring and cusps area cross-sectional echocardiographic analysis to detect aortic valve prolapse requires meticulous review of the real time study. The redundancy of a cusp with diastolic motion towards the left ventricular outflow tract has been our operational definition of aortic valve prolapse. The sensitivity and specificity of this technique cannot be evaluated due to the lack of a gold standard for prolapse valves but we

believe that the abnormal aortic valve morphology and motion characteristics in our subgroup of patients with mitral valve prolapse when compared to controls is an acceptable definition for this entity. Further support is provided by the increased prevalence of aortic root dilatation and clinical aortic insufficiency in this subgroup of patients.

Six of our 17 patients with aortic valve prolapse had aortic cusp eccentricity probably due to myxomatous degeneration affecting one cusp more severely. These patients must be differentiated from those with congenital bicuspid aortic valve disease. In bicuspid aortic valve disease one cusp is usually larger and has been called the 'conjoined cusp'. The conjoined cusp may prolapse on the basis of excessive tissue relative to the distance between the two commissural attachments. The differentiation between aortic valve prolapse on the basis of the floppy valve syndrome or bicuspid aortic valve disease⁹ may be possible using the short axis view of cross sectional echocardiography. Using this view the presence of three separate aortic cusps would tend to exclude the presence of a bicuspid valve and in fact all six of our patients with an eccentric aortic cusp had three aortic valve cusps using this approach. This unfortunately does not entirely prove the absence of a bicuspid aortic valve since an uncommon form of congenital bicuspid aortic valve exists in which the center of the free edge of the conjoined cusp is joined to the aortic wall by a thin strand. This might give the impression of a tricuspid aortic valve.¹⁰ However since our patients were drawn from a population of patients with mitral (and often tricuspid) valve prolapse and since all six did have an apparent tricuspid valve on the short axis view and one patient had a tricuspid aortic valve on angiography we believe the majority if not all of these cases did in fact have aortic valve prolapse on the basis of the floppy valve syndrome.

In addition this study suggests that not only congenital bicuspid aortic valves may cause eccentricity of the aortic valve closure line in diastole on M mode echocardiography¹¹ but that aortic valve prolapse caused by the floppy valve syndrome should be considered. Though not statistically significant the increased prevalence of tricuspid valve prolapse in patients with aortic valve prolapse suggests that a more widespread involvement of the myxomatous degenerative

Mitral valve prolapse in anxiety neurosis (panic disorder)

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The typical symptoms of anxiety neurosis or panic disorder—palpitation, dyspnea, chest pain, and dizziness—suggest a cardiovascular disturbance and in the past led to such labels as irritable heart, "effort syndrome," and neurocirculatory asthenia.¹ Similar symptoms may be reported by patients with the recently described syndrome of mitral valve prolapse. In fact, panic disorder and mitral valve prolapse share a number of clinical features. Both are common disorders, probably affecting 5% to 10% of the population, both are frequent in young women, and both may be familial.² The characteristic physical findings of mitral prolapse—a mid-systolic click and late systolic murmur—have not been associated with panic disorder in the past, but these sounds were in general not felt to be of clinical significance until Barlow and co-workers³ demonstrated their relationship to the prolapsing mitral valve.

The similarities between panic disorder and mitral valve prolapse and Wooley's⁴ hypothesis suggest that many patients with mitral valve prolapse might be panic disorder patients.

and associates⁴ described several such cases. The purpose of this study was to test Wooley's hypothesis in a group of rigorously diagnosed patients with panic disorder.

Methods

From 112 anxiety neurosis patients followed by Noyes and Clancy,⁵ we selected 20 patients for this study on the basis of (1) meeting Feighner and colleagues' research criteria for anxiety neurosis (panic disorder) and (2) for convenience living within 100 miles of Iowa City. Feighner and colleagues' criteria for the diagnosis of anxiety neurosis (panic disorder) are (1) age of onset prior to 40, (2) chronic nervousness with recurrent anxiety attacks (manifested by apprehension, fearfulness or sense of impending doom) occur at times other than during marked physical exertion or life-threatening situations and in the absence of medical illness or other psychiatric illness. There must have been at least six anxiety attacks, each separated by at least a week from the others, and (3) at least four of the following symptoms: (a) dyspnea or a choking or smothering sensation, (b) palpitations, (c) chest pain or discomfort, (d) dizziness, (e) paresthesia. All 20 patients who met these criteria and lived within 100 miles of Iowa City were contacted and all agreed to participate. One family was doubly ascertained through a mother and daughter both with panic disorder, leading to a total of 21 index subjects. These 15 women and six men ranged in age from 21 to 62 years with a median of 37. An

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Table 1

| | AN (N = 21) | Control (N = 20) | P |
|---|----------------|---------------------|-------|
| <i>Comparison of anxiety neurosis vs control subjects</i> | | | |
| (a) Systolic click and/or murmur | 10 | 6 | NS |
| (b) ECG resting ST T abnormalities | 7 | 0 | <0.01 |
| (c) ECG PVCs during exercise | 9 | 1 | <0.01 |
| (d) Echocardiographic prolapse | 8 | 2 | <0.05 |
| (e) Echo prolapse plus (a) | 5 | 1 | NS |
| (f) Echo prolapse plus (a) or (b) | 7 | 1 | <0.05 |
| <i>Echocardiographic diameters†</i> | | | |
| (g) Left ventricular end diastolic diameter (cm) | 44 ± 0.6 | 49 ± 0.8 | NS |
| (h) Left ventricular end systolic diameter (cm) | 29 ± 0.4 | 31 ± 0.8 | NS |
| (i) ΔD | 0.36 ± 0.07 | 0.38 ± 0.08 | NS |
| (j) Left atrial diameter (cm) | 29 ± 0.4 | 31 ± 0.6 | NS |

P values are Fisher exact one tailed

†Values ± 1 standard deviation

ΔD = fraction of minor axis shortening

prolapse plus click murmur and/or exercise induced PVCs. Within the panic disorder group patients with mitral valve prolapse determined by echocardiogram and those without prolapse had a similar incidence of clicks and/or murmurs and electrocardiographic abnormalities.

Discussion

In this study eight of 21 panic disorder patients had echocardiographic evidence of mitral prolapse. Seven of these had auscultatory or electrocardiographic findings suggestive of the mitral prolapse syndrome in addition to echocardiographic demonstration of prolapse. Of the two control subjects with echocardiographic evidence of prolapse only one showed additional abnormalities on auscultation or electrocardiogram. Thus mitral prolapse was identified significantly more often among the panic disorder patients than among the controls ($p < 0.05$). This finding suggests that a substantial number of patients bearing the psychiatric diagnosis of panic disorder also have an organic abnormality mitral valve prolapse.

The panic disorder patients in this study were selected solely on the basis of meeting diagnostic criteria for panic disorder and also by geographic proximity to the medical center. However they were part of a larger group which had originally been selected from patients referred to the University of Iowa Clinics. This raises the question of whether the larger group contained patients with abnormal cardiac findings who might have been preferentially referred for evaluation. The possibility of such a selection bias was assessed by reviewing the original patient records. This revealed that most had been referred to the Internal Medicine and Neurology Clinics for evaluation of symptoms which their referring physician thought might have been associated with physical disease. Heart murmurs were noted at the time of the original evaluation in only four patients and none were considered at that time to have symptoms of cardiac origin.

Although we were able to demonstrate prolapse in many of these panic disorder patients the simultaneous occurrence of these conditions does not necessarily imply a causal relationship. Why patients with mitral prolapse develop symptoms such as chest pain, dyspnea and palpitations cannot at this time be answered. It is conceivable that both panic disorder and mitral prolapse are manifestations of some underlying disorder as yet undefined.

Although this study is a preliminary one the results support the link between anxiety neurosis or panic disorder and the mitral valve prolapse syndrome as proposed by Wooley.⁴ Patients with symptoms of panic attacks should be suspected of having the mitral prolapse syndrome. Echocardiography, electrocardiography and stress testing are diagnostically useful in such patients.

Summary

Our purpose was to determine the incidence of mitral valve prolapse in patients with anxiety neurosis or panic disorder with symptoms including recurrent anxiety attacks, dyspnea, palpitations, chest pain, dizziness and paresthesias. Twenty-one patients and 20 age and sex matched normal controls were studied. Objective cardiac abnormalities were significantly ($p < 0.05$) more frequent in the patient group as compared to the control group. These comprised echocardiographic prolapse, ST-T abnormalities,

age and sex matched control group was selected from hospital employees. There were 14 women and 14 men with a median age of 37 (range 23 to 62 years). This group was specifically free of anxiety symptoms and denied a history of heart disease.

The study was approved by the Human Research Committee of the University of Iowa. Informed written consent was obtained from all participants.

A medical history was obtained from all subjects with specific questioning for symptoms of panic disorder. A physical examination was performed by a cardiology fellow. During the cardiovascular examination, systolic clicks and murmurs were sought by auscultation in the supine and upright positions. Resting and exercise electrocardiograms were obtained using the Bruce exercise protocol. Echocardiograms were performed on all patients using a Smith Kline Ekoline 20A ultrasonoscope with a 2.5 MHz transducer focused at 7.5 cm and a Honeywell 1856 fiberoptic strip chart recorder. The mitral valve recordings were obtained by positioning the transducer perpendicular to the chest wall as recommended by Popp and co-workers.

The echocardiographic criteria for mitral prolapse were those of Marikiewicz and colleagues.¹ The points of coaptation (C point) and separation (D point) were identified and a line was drawn between the two (C-D line). Echocardiographic prolapse was considered to be present if the predominant systolic mitral echo extended more than 2 mm posteriorly from the C-D line either in a smooth concave hammock shaped fashion (holosystolic prolapse) or as a sharp mid late systolic buckling. The echocardiograms were read by an observer who was not otherwise involved in the study and who did not know if the recording was from an index subject or a control.

Left ventricular diameters were measured at end diastole (R wave of ECG) and end systole (smallest distance between posterior wall and septum). Left atrial diameters were measured at end systole.

Results

The results are summarized in Table I. Ten panic disorder patients had systolic clicks and/or murmurs on auscultation. Of these murmurs, two were holosystolic, five were mid late systolic, one was early systolic, and one was variable between

examinations. Two patients had mid late systolic clicks (one of these also had a murmur). No patient had skeletal abnormalities associated with mitral valve prolapse such as pectus excavatum.

Seven patients showed ST-T wave abnormalities on resting electrocardiograms; two of these seven patients were taking tricyclic antidepressant drugs which may have caused or contributed to these electrocardiographic findings. No patient developed angina or ST-T changes with exercise, all but one achieved 80% of the age predicted maximum heart rate. One patient had premature ventricular contractions (PVCs) at rest, nine had PVCs with exercise (one had PVCs occurring in couplets during exercise).

Systolic prolapse was demonstrated by echocardiogram in eight panic disorder patients: four holosystolic and four mid late systolic. Of the eight panic disorder patients with echocardiographic evidence of prolapse, five had clicks and/or murmurs and two others had PVCs on exercise. Only one patient with echocardiographic evidence of prolapse had no additional abnormalities.

Six control subjects had systolic clicks and/or murmurs (Table I). On auscultation, two had holosystolic murmurs and one had a mid late systolic murmur. Four patients had mid late systolic clicks (one of these also had a murmur). One control subject had PVCs at rest and another developed them with exercise. Three control subjects developed ST-T changes with exercise but none experienced angina. Two had echocardiographic evidence of prolapse: one holosystolic and one mid late systolic. Of these two control subjects with evidence of prolapse, one had a systolic click and resting PVCs while the other had no additional abnormalities.

Echocardiographically determined left ventricular and left atrial volumes and left ventricular minor axis shortening (ΔD) were normal for both groups. There were no significant differences between the groups in these measurements.

Differences between groups were assessed for significance using Fisher's exact test or in the case of echocardiographic diameters, a Student's *t* test was used (Table I). Patients with panic disorder had a significantly higher incidence of echocardiographically demonstrated prolapse, resting electrocardiographic ST-T abnormalities, exercise induced PVCs and echocardiographic

Evaluation of left atrial thrombus with computed tomography

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Detection of intra atrial thrombi in patients with mitral valvular diseases is very important in determining the application of anticoagulant therapy or surgical treatment. Angiographic and echocardiographic evaluations of left atrial thrombi have been reported^{1,2} but small thrombi located in the left atrial appendage have been associated with difficulties in detection by conventional methods.^{1,2} On the other hand preliminary reports on the possible application of computed tomography in the field of cardiology have recently become available.³⁻⁶ Harada and associates³ have demonstrated the possibility of detecting left atrial thrombus with computed tomography. The present study was intended to show the usefulness of computed tomography in the evaluation of left atrial thrombi.

Materials and methods

Twenty three patients with mitral valvular diseases were studied (nine with mitral stenosis, three with mitral regurgitation and 11 with mitral stenosis regurgitation). Thirteen of these

cases subsequently underwent cardiac surgery and two of them had autopsy. A computed tomographic whole body scanner which utilizes continuously rotating gantry and pulsed and with x ray radiation collimated to form a thin fan shaped beam was used.^{4,5} A complete section scan was performed in 3 seconds. The scale: x ray transparency (CT number) was -1000 for air, 0 for water and +1000 for bone. To protect the quality of the tomograms gated computed tomographic scanning to obtain stop action images⁶ was not applied in the present study. All computed tomograms were obtained in the position of deep inspiration. Sustained enhancement was obtained with a rapid intravenous infusion of 30% meglumine iohalamate (200 to 300 ml).

Results

Left atrial thrombi were revealed in the following three cases and were compared with the surgical or postmortem findings.

Patient 1 A 45 year old woman presented with auscultatory findings compatible with mitral stenosis regurgitation and tricuspid regurgitation. She had at least two well documented histories of bilateral heart failure and had been placed on digitalis and furosemide for the past 5 years. She did not have any episode suggestive of systemic embolization. Electrocardiograms showed right ventricular hypertrophy and atrial fibrillation. Echocardiographic (UCG) and two dimensional

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Varian Computed Tomographic Whole Body Scanner

on resting ECG premature ventricular contractions on exercise ECG and the combination of echo prolapse with clicks/murmurs or exercise-induced PVC. We conclude that patients with anxiety neurosis or panic disorder may also have evidence of an organic abnormality—the mitral prolapse syndrome.

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IMPORTANT INFORMATION FOR AUTHORS

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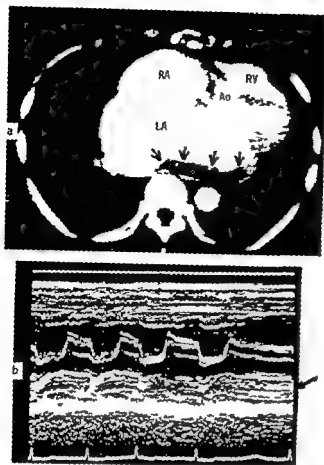


Fig 3 A patient with mitral stenosis-regurgitation, atrial fibrillation and two histories of cerebral thromboses (Case No 3) A computed tomogram at the level of the left atrium a thrombus (75 cm \times 17 cm \times 3 cm) is indicated by arrows RA = right atrium RV = right ventricle Ao = aorta LA = left atrium B echocardiographic findings in the same patient (the thrombus is indicated by an arrow)

Hg pulmonary capillary wedge—15 mm Hg (mean) and aorta—106/64 mm Hg

The left ventricle was not entered via the retrograde route due to severe aortic stenosis. Cineangiographic findings (levophase pulmonary arteriography and aortography) revealed mitral stenosis, aortic stenosis with regurgitation and enlarged left atrium. There was an insufficient filling of the left atrial appendage which suggested a thrombus in the area of the left atrial appendage.

Computed tomograms at the left atrial level revealed two spherical thrombi—one located at the atrial appendage with a tomographically measured size of 20 cm \times 23 cm and another located at the right posterior wall of the left atrium with a measured size of 20 cm \times 29 cm (Fig 2). She was operated on for valve replace-

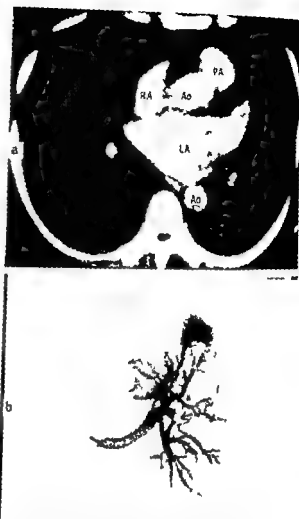


Fig 4 A patient with mitral stenosis regurgitation at fibrillation and a history of renal thrombosis. There is a thrombus lodged in the dorsal branch of the left renal artery as indicated by an arrow (B) but there is no left atrial thrombus demonstrated with computed tomography (A). C diac surgery subsequently performed also revealed no left atrial thrombus RA = right atrium Ao = aorta PA = pulmonary artery LA = left atrium

ment and a total of 20 gm of left atrial thrombi which were consistent with the shapes and sizes detected by computed tomographic method, was excised.

Patient 3 A 68 year old woman presented with mitral stenosis regurgitation, atrial fibrillation and with two previous episodes of cerebral thromboses and another episode of bilateral femoral arterial thrombosis. Right heart catheterization was performed and intracardiac pressures were as follows: right atrium—5 mm Hg (mean), right ventricle—40/5 mm Hg, pulmonary artery—52/30 (mean 30) mm Hg and pulmonary capillary wedge—26 mm Hg (mean). A levophase pulmo-



Fig 1 A patient with mitral stenosis regurgitation, tricuspid regurgitation, and atrial fibrillation (Case No 1) A computed tomogram at the level of the left atrium a thrombus (13 cm \times 16 cm) is indicated by an arrow RA = right atrium RV = right ventricle Ao = aorta LA = left atrium B surgically excised thrombus of the same patient (35 gm)



Fig 2 A patient with mitral stenosis regurgitation aortic stenosis regurgitation atrial fibrillation and a history of cerebral thrombosis (Case No 2) A computed tomogram at the level of the left atrium a thrombus (9.0 cm \times 2.3 cm) is shown by an arrow at the atrial appendage B another thrombus (9.0 cm \times 2.9 cm) is indicated by an arrow at the right posterior wall of the left atrium which is 7 cm lower than the appendage level SVC = superior vena cava Ao = aorta PA = pulmonary artery LA = left atrium

findings of the patient were compatible with mitral stenosis minimal regurgitation and tricuspid regurgitation but no left atrial thrombus was detected echocardiographically

Intracardiac pressures were as follows right atrium—6 mm Hg (mean) right ventricle—90/7 mm Hg pulmonary artery—97/37 (mean 58) mm Hg pulmonary capillary wedge—24 mm Hg (mean) left ventricle—124/13 mm Hg and aorta—129/79 mm Hg Cineangiographic findings (levophase of pulmonary angiogram and left ventriculogram) revealed thickened and stenosed mitral valves grade 1 mitral regurgitation, and a markedly enlarged left atrium but no thrombus was detected cineangiographically

On the other hand computed tomography at the level of the left atrium indicated a filling defect in the left atrial appendage measured as 13 cm \times 16 cm on the tomogram (Fig 1a)

Open mitral commissurotomy was performed 4 days after the computed tomographic evaluation and a well-organized thrombus of 1 cm \times 15 cm \times 2 cm (weight 35 gm) was found in the left atrial appendage and was excised (Fig 1b)

Patient 2 A 47 year old woman presented with mitral stenosis regurgitation aortic stenosis regurgitation and atrial fibrillation She had a history of cerebral thrombosis a year ago with persistent right hemiplegia Phonocardiographic and echocardiographic findings were compatible with the above diagnoses and the presence of left atrial thrombi was suspected echocardiographically Intracardiac pressures were as follows right atrium—4 mm Hg (mean) right ventricle—34/3 mm Hg pulmonary artery—35/16 (mean 23) mm

results with computed tomography in 13 patients who subsequently underwent cardiac surgery. Computed tomography is essentially noninvasive and appears to be one of the best methods to evaluate left atrial thrombus.

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nary arteriogram revealed an enlarged left atrium with a thrombus located at the posterior wall of the left atrium

Computed tomographic findings demonstrated a large left atrial thrombus measuring 7.5 cm \times 1.7 cm (the height was estimated as an average of 3 cm) located at the posterior wall of the left atrium (Fig 3a). The thrombus attached to the posterior wall of the left atrium was easily demonstrated echocardiographically as shown in Fig 3b. The computed tomographic findings were confirmed by autopsy performed 3 months after the tomographic evaluation and the weight of the thrombus was approximately 40 gm.

Discussion

Detection of left atrial thrombi in patients with mitral valvular diseases is of significant importance regardless of the size of the thrombi because the patients are always faced with the possibility of systemic embolization. Parker and colleagues have demonstrated that atrial thrombi were predicted correctly angiographically in six out of 70 patients who subsequently had cardiac surgery but thrombi could not be detected in two patients. Echocardiography is noninvasive and one of the most hopeful methods for detecting atrial thrombi in patients with mitral valvular diseases.

Recently Mikell and associates demonstrated atrial thrombi correctly by two dimensional echocardiography and the minimum thrombus detected echocardiographically as a spherical aggregate approximately 1.5 cm in diameter.

On the other hand due to the limitation in the direction of echo beam projection small thrombi located in the left atrial appendage or in the right edge of the left atrium are difficult to detect echocardiographically. Computed tomography has the advantage of offering uniform slices of the left atrium in an attempt to detect thrombi in unknown areas of the left atrium. The method is not disturbed by the presence of the ribs or thoracic cage as in the case of echocardiography.

Both fresh and organized thrombi were delineated with computed tomography and the nature of the thrombi might be possible to estimate by the difference in the x ray transparency i.e. the CT numbers. In Case No. 1 the thrombus was mostly organized with partial fibrosis and the CT number was +68. In Case 2 the thrombi were

almost fresh without fibrosis and the CT number was +42 which was identical to that of the left ventricular chamber (+40). The CT number was not recorded in Case 3.

The minimum size of the thrombi detected tomographically was 3.5 gm as shown in Case 1 but the lowest limit of the thrombus size which can be detected is still not known although there is the possibility that an extremely small thrombus might be missed by any method. In another 51 year old woman with mitral stenosis regurgitation and atrial fibrillation an episode of renal thrombosis was encountered 6 days before the tomographic evaluation and a thrombus 0.2 cm \times 0.4 cm in size and lodged in the dorsal branch of the left renal artery was demonstrated angiographically.

However there was no left atrial thrombus apparent in computed tomography and cardiac surgery performed subsequently did not reveal a left atrial thrombus which appeared to have been washed out completely (Fig 4). Therefore there have been no false negative or false positive cases experienced so far.

The stop action method gated with ECG is possible in the system used in the present study but our impression is that the quality of the tomogram is not satisfactory due to reduced data sampling numbers for every frame of the tomogram. Therefore it should be noted that the configurations of the various cardiac structures obtained by computed tomography are affected by the effects of cardiac movements. Fortunately however the cardiac movements are relatively limited at the cardiac base especially in enlarged atria with fibrillation.

Computed tomography is a noninvasive method and based on our experience in a limited number of patients it appears to be one of the best methods in evaluating left atrial thrombi to determine the details necessary for medical or surgical treatment.

Summary

Left atrial thrombi were evaluated with computed tomography in 23 patients with mitral valvular diseases. In three of the patients left atrial thrombi were delineated with computed tomography and were confirmed by cardiac surgery or autopsy. The minimum size of the thrombi detected tomographically was 3.5 gm.

There were no false positive or false negative

Table I Analysis of survivors, nonsurvivors and mortality rates according to age by decade of life and by sex

| Age group | No of survivors | | No of non survivors | | % mortality | | total mortality |
|-----------|-----------------|--------|---------------------|--------|-------------|--------|-----------------|
| | Male | Female | Male | Female | Male | Female | |
| Group B | | | | | | | |
| 30-39 | 29 | 4 | 0 | 0 | 0 | 0 | 0 |
| 40-49 | 90 | 24 | 6 | 1 | 6.3 | 4.0 | 5.8 |
| 50-59 | 212 | 57 | 17 | 6 | 7.4 | 9.5 | 7.8 |
| 60-69 | 192 | 101 | 21 | 12 | 9.9 | 10.6 | 10.1 |
| Total | 523 | 186 | 44 | 19 | 7.8 | 9.3 | 8.2 |
| Group A | | | | | | | |
| 70-79 | 50 | 38 | 10 | 23 | 26.5 | 37.7 | 31.8 |
| 80-89 | 10 | 20 | 4 | 10 | 28.6 | 33.3 | 31.8 |
| 90-99 | 0 | 1 | 1 | 0 | 100 | 0 | 50.0 |
| Total | 60 | 59 | 23 | 33 | 27.7 | 35.9 | 32.0 |

Table II Prevalence of various prognostic factors and the mortality risk of each prognostic factor in survivors and nonsurvivors

| Prognostic factor | % prevalence in study group (Group A) | No of survivors | No of non survivors | % mortality | p value |
|----------------------------|---------------------------------------|-----------------|---------------------|-------------|---------|
| History of angina pectoris | 54.3 | 64 | 31 | 32.6 | 0.84 |
| Hypertension | 44.0 | 53 | 24 | 31.2 | 0.91 |
| History of prior MI | 33.1 | 39 | 19 | 37.8 | 0.87 |
| History of CHF | 20.0 | 23 | 12 | 34.3 | 0.7 |
| Diabetes mellitus | 21.7 | 23 | 15 | 39.5 | 0.74 |
| Total | | 119 | 56 | | |

Abbreviations MI = myocardial infarction CHF = congestive heart failure

of life for all patients admitted during the study period. The over all mortality rate for the elderly group was 32%. There was no difference between the mortality rate for the 70 to 79 year age group (31.8% mortality) and the 80 to 89 year age group (31.8% mortality). The mortality rate for all elderly females studied was 35.9% as compared to 27.7% for all elderly males (Table I). This was not statistically significant ($p = 0.25$ by Chi square analysis). There were 772 patients below age 70 admitted during the same time frame that were analyzed for mortality related to age and sex (Group B). Table I shows that the over all mortality rate was 0 below age 40 and increased progressively for each decade of life. This was true for both men and women. Women had a slightly higher mortality rate for each decade after age 49. The total mortality rate for men under age 70 was 7.8% for women it was 9.3% and for the total group it was 8.2%.

The following prognostic factors were studied in the elderly group to determine their association with prognosis: a history of angina pectoris, myocardial infarction (MI), hypertension, congestive heart failure (CHF) or diabetes mellitus. The prevalence of each of the above potential prognostic factors in the group was: history of angina pectoris 54.3%, history of MI 33.1%, history of hypertension 44.0%, history of CHF 20.0% and history of diabetes mellitus 21.7% (Table II). No single prognostic factor was associated with a significant increase in mortality rate during the hospital course.

The mortality rate of patients with no prognostic factors was 24.3%. With one prognostic factor it was 41%, with two prognostic factors it was 25.5%, with three prognostic factors it was 42.4% and with four prognostic factors it was 25.7% (Table III). There was no associated increase in mortality rate with an increase in the number of prognostic

Acute myocardial infarction in hospitalized patients over age 70

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Although the clinical course and prognosis of patients with acute myocardial infarction has been carefully studied, little attention has been given to the effect of age on mortality rate.

In this paper we present the age, sex, and hospital mortality rate and analyze the factors influencing prognosis in a group of patients aged 70 years and older with acute myocardial infarction. A comparison is made with the mortality rate of all patients less than 70 years of age who were admitted during the same time period.

Patients and methods

The elderly study group (Group A) included all patients admitted to the coronary care unit of Piedmont Hospital between May 1, 1971 and January 31, 1977 who met the following criteria:

1. age 70 years or greater
 2. a diagnosis of acute myocardial infarction (MI) on the basis of any two of the following three factors:
 - a. prolonged chest discomfort compatible with myocardial injury
 - b. characteristic electrocardiographic changes of myocardial infarction including serial ST-T changes or the development of pathologic Q waves
 - c. elevation of serum creatine phosphokinase (CK) to at least two times the upper limits of the normal range
- A total of 175 patients met two or more of these

criteria. All patients were observed in the coronary care unit with continuous monitoring. No drugs were given routinely without specific indications. Data were obtained in a retrospective manner from a comprehensive data base acquired at the time of admission on all patients to the coronary care unit as well as from a review of physician's office records prior to admission. A prior history of angina pectoris, myocardial infarction, diabetes mellitus, hypertension (systolic BP equal to or greater than 160/90 mm Hg) and congestive heart failure was noted. The physician's office records did not always contain the physician's specific diagnostic criteria; therefore this information was considered as historical information and consequently does not meet rigid standards of definition. Serial electrocardiograms (ECGs) were evaluated to determine the electrocardiographic site of the myocardial infarction and the presence or absence of a conduction defect. Shock was defined as a systolic blood pressure of 90 mm Hg or less associated with a urine output of less than 20 cc/hr. Complications occurring during the AMI were determined from a review of the hospital record, the detailed data base compiled during the admission, and a review of all ECGs and chest films reports. The cause of death was determined from the hospital record or autopsy reports.

Group B was composed of 772 patients below age 70 with acute MI who were admitted to the hospital during the same time period. The age and sex related hospital mortality rate of this younger age group was compared with the study group.

Results

There were 175 patients in Group A—83 (47.4%) were male and 92 (52.6%) were female. Table I shows the age, sex, and mortality rate per decade.

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of the deaths due to anterior MI. The major cause of death in the 16 patients with inferior MI was shock in four patients (25%) and sudden death in three (18.8%) accounting for 43.8% (seven of 16) of the 16 deaths due to inferior MI.

The ten patients with autopsy documented external cardiac rupture had several distinguishing characteristics. The sex was predominantly female (seven of 10). Nine of the ten patients had no history of prior MI. The cardiac rupture generally occurred during the first 48 hours of hospitalization (seven of 10) and was within 60 hours of the onset of symptoms in the seven cases. There were seven ruptures of the anterior wall, two of the inferior wall, and one rupture of the apex. This distribution paralleled the distribution of the myocardial infarctions in the entire study group (anterior MI 66.9%, inferior MI 33.1%, Table IV). The location of the external myocardial rupture was always in the site of the acute myocardial infarction as determined by ECG and as noted at autopsy.

There were nine patients who died suddenly without autopsy. Four of these nine patients sustained a final clinical event that was marked by sudden cardiorespiratory arrest with a bradycardia observed on the ECG monitor and with absent pulses on physical examination. Myocardial rupture was suspected in these four patients. The remaining five patients who died suddenly were not monitored at the time of death and the cause of the final event was not apparent.

Discussion

Patients with myocardial infarction in the age group 70 and older differ in their sex distribution, clinical course, and hospital mortality rate when compared to patients younger than age 70. In this study of 175 patients aged 70 and older, the male:female ratio was 0.9:1.0 (Table I). In contrast, the male:female ratio of our 772 patients under age 70 admitted during the same time period was 2.77:1.0, while under age 60, the male:female ratio was 3.85:1.0. In reported series of patients less than 70 years of age, there is a striking male preponderance. Fitzgerald² studied 865 patients with acute MI and found the male:female ratio to be 7:1 below age 50, 10:1 between age 50 and 59, and 4:1 in the age group 60 to 69. Following a peak in the sixth decade, male preponderance declines rapidly until the eighth decade when the male:female ratio approaches 1:1 in most large series.¹

The prevalence of certain prognostic factors in the age group 70 years and older is higher than the incidence of similar factors reported in younger age groups. Frank³ studied 881 men aged 25 to 64 who had their first MI. The incidence of angina pectoris was 17%, hypertension was 25%, congestive heart failure was 4%, and diabetes mellitus was 11%.³ In our elderly group of patients, the incidence of angina pectoris was three times, hypertension was 1.8 times, congestive heart failure was five times, and diabetes mellitus was two times the incidence in the study by Frank (Table IV). A history of prior MI was present in 33.3% of our patients. This is similar to the 28% to 38% prevalence of prior MI reported in several studies of younger patients.⁴⁻¹⁰

The increased prevalence of these prognostic factors in our elderly group was not however associated with an increased mortality rate (Table II). There were no prognostic factors present in 23.5% of the survivors or in 16.1% of the nonsurvivors (Table III). The mortality rate of patients with zero, one, two, three, and four prognostic factors represented a random distribution (Table III). Hospital mortality rate was not influenced by the number of prognostic factors present in individual patients (Table III), nor by the overall prevalence of prognostic factors in the entire study group (Table II).

Factors that significantly influenced hospital mortality rate from acute MI were the development of shock, pulmonary edema on chest x-ray, a clinical diagnosis of congestive heart failure, and the development of complete heart block or new bundle branch block during the hospital course ($p \leq 0.01$, Table IV). These complications are usually associated with the loss or dysfunction of a significant amount of ventricular muscle from the new or any prior MI. In this study, there was a significantly high mortality rate of 88.9% associated with complete heart block ($p = 0.001$, Table IV). Although all three of the patients with new BBB died, the hospital mortality rate associated with the presence of BBB in general, including BBB known to be present prior to the acute myocardial infarction, was not significantly increased ($p = 0.26$, Table IV). This discrepancy may be due to the high incidence of pre-existing BBB on the basis of Lev's or Lenegre's disease in the elderly.¹¹⁻¹³ Bundle branch block related to these causes may not signify the same degree of muscle necrosis or ventricular dysfunction as BBB resulting from acute myocardial infarction.

tic factors per patient ($p = 0.25$ by Chi square analysis)

Hospital course The serial ECGs and hospital course of the 175 elderly patients were reviewed to determine whether or not factors could be identified which were associated with increased hospital mortality rate. The mortality rate of patients with anterior MIs (32.7%) was not significantly different from that of patients with inferior MIs (30.2% Table IV). The development of either complete heart block or a new bundle branch block on the ECG was associated with a high mortality rate (Table IV). Eight of the nine patients (88.9%) with complete heart block died despite temporary cardiac pacing. Complete heart block was associated with an anterior MI in five patients (55.6%), inferior MI in three patients (33.3%), and an undetermined site in one patient. Twenty-one patients had a bundle branch block, a right bundle branch block (RBBB) was present in ten and a left bundle branch block (LBBB) was present in 11 (Table IV). The development of a new bundle branch block (BBB) during the hospital course was documented in only three patients (1.7%) all of whom died. There were 18 patients with BBB on the admission ECG, nine of these 18 cases could be documented as being present previously. On admission to the hospital one patient had a LBBB which subsequently resolved. The remaining eight cases of BBB were of unknown duration. The mortality rate of all patients with old or new BBB was 42.9% (nine of 21). Five of the 56 patients who died had RBBB and four had LBBB.

Cardiogenic shock, pulmonary edema on chest x-ray, CHF by examination and complete heart block occurring on admission or during the hospital course were all associated with a significant mortality rate ($p < 0.01$ Table IV). The presence of shock either on admission or developing during the hospital course was associated with an 80% mortality rate (24 of 30). Pulmonary edema documented on chest x-ray and occurring at any point during the hospital course was associated with a 60% mortality rate (15 of 25). Congestive heart failure (CHF) as defined by rales, jugular venous distention and/or a ventricular gallop was associated with a mortality risk of 39.6% (42 of 106).

Hospital deaths The records of the elderly patients dying in the hospital were analyzed to determine the specific cause of death (Table V). The overall hospital mortality rate was 32% (56 of 175). The major cause of death was shock,

Table III Comparison of the number of prognostic factors in survivors and nonsurvivors

| | Number of prognostic factors | | | | | | |
|---|------------------------------|------|------|------|-----|-----|-------|
| | 0 | 1 | 2 | 3 | 4 | 5 | Total |
| Survivors | | | | | | | |
| No | 28 | 23 | 38 | 19 | 9 | 2 | 119 |
| % | 23.5 | 19.3 | 31.9 | 16 | 7.6 | 1.7 | |
| Non survivors | | | | | | | |
| No | 9 | 16 | 13 | 14 | 3 | 1 | 56 |
| % | 16.1 | 28.6 | 23.2 | 25 | 5.4 | 1.8 | |
| % mortality according to the number of prognostic factors present | 43 | 41 | 23.5 | 42.4 | 25 | | |

accounting for 33.9% (19 of 56) of the deaths. Of the 19 patients who died of shock, 13 of 19 had anterior infarctions (68.4%), four of 19 had inferior infarctions (21.1%) and two of 19 had an undetermined site of infarction (10.5%). Mitral regurgitation was present in three of the four patients with shock related to an inferior infarction. The inferior MI was associated with a prior anteroseptal MI in the remaining patient.

External cardiac rupture was documented in 10 of 23 patients studied at autopsy (Table V). This represented 17.9% of the 56 deaths and was the second major cause of death. Sudden death (unwitnessed and unmonitored) accounted for an additional nine deaths representing 16% of the total mortality. A significant number of these deaths may have been cardiac rupture (discussed below) however autopsies were available on only two of the nine. The remainder of the deaths were due to severe CHF (six patients—10%), arrhythmia (four patients—7.1%), GI bleeding (two patients—3.6%), aspiration (one patient—1.8%) and aortic dissection (one patient—1.8%). Two patients (3.6%) one with an anterior and one with an inferior MI developed ventricular septal rupture and both died postoperatively following surgical repair. The cause of death could not be determined from the record in two cases (3.6% Table V).

The major cause of death in the 35 patients with anterior MI was extensive muscle damage. This was manifested by shock in 13 of the 35 cases (37.1%) and severe CHF in five of the 35 cases (14.3%) (Table V) accounting for 51.4% (18 of 35)

Table V Causes of death related to electrocardiographic site of infarction

| Cause of Death | Ant MI | Inf MI | LBBB | Total no | % of deaths |
|-----------------------------|---|--------|------|----------|-------------|
| Shock | 13 | 4 | 2 | 19 | 33.9 |
| Cardiac rupture | 8 | 2 | | 10 | 17.9 |
| Sudden death | Sudden loss of consciousness associated with respiratory arrest bradycardia and absent pulses | 3 | 1 | 4 | 7.1 |
| | Sudden death of unknown cause | 2 | 3 | 5 | 8.9 |
| Severe CHF | 5 | 1 | | 6 | 10 |
| Arrhythmia | 3 | 1 | | 4 | 7.1 |
| GI bleeding | | 2 | | 2 | 3.6 |
| Aspiration | | 1 | | 1 | 1.8 |
| Aortic dissection | | 1 | | 1 | 1.8 |
| Ruptured ventricular septum | 1 | 1 | | 2 | 3.6 |
| Unknown | | | 2 | 2 | 3.6 |
| Total non survivors | 35 | 16 | 5 | 56 | 100 |

MI = myocardial infarction CHF = congestive heart failure LBBB = left bundle branch block GI = gastrointestinal Ant = anterior Inf = inferior

of cardiac rupture. The incidence of cardiac rupture in documented acute MIs has been reported to be 3.8% to 27%.²¹⁻²⁶ Most series have reported an average incidence of about 10%.^{21-23, 26} An increased incidence of cardiac rupture has been found in the elderly and in females.²⁴⁻²⁶ The majority of cardiac ruptures are reported to occur during the first 3 days following the onset of the symptoms of acute MI.^{22-23, 26} Cardiac rupture occurred during the first 48 hours of hospitalization and within 60 hours of the onset of symptoms in 70% of our autopsy-documented cases. In this study 70% of the patients with cardiac rupture had definite transmural MIs and the remaining 30% had acute MIs of undetermined extent at the time of death from cardiac rupture. The association of external cardiac rupture with a first MI (nine of 10 patients in this study) is attributed to the absence of significant collateral vessels and fibrosis in the area of acute infarction where the rupture develops.²⁷

The hospital mortality rate from an acute MI in the elderly group of 175 patients was 32% (Table I). This was 3.9 times greater than the mortality rate of 8.2% in our younger group. The mortality rate reported in several studies in the literature for predominantly younger hospitalized patients with MI (age 70 and younger) is 8% to

20% (average 15%).^{1, 21-23, 26} The explanation for the increased mortality rate in the elderly has not been well defined. There is a higher incidence of associated prognostic factors (e.g., previous MI, shock, CHF, etc.) in elderly patients. Russek and Zohman²⁸ divided patients above and below 60 years of age into good risk and poor risk groups. Two thirds of the patients 60 years and older were shown to be poor risks compared to 47% of patients less than 60 years of age.²⁸ There was no significant difference in mortality rate between the older and younger groups when the

risk factors were comparable. Russek and Zohman concluded that age itself was not an independent risk factor. Our findings differ from theirs and indicate that age is a significant independent prognostic factor. When the mortality rate in our good risk elderly group (patients with no prognostic factors, Table III) is compared to the mortality rate of our younger patients (Group B) with and without prognostic factors, the mortality rate in the good risk older age group is 2.7 times that of the entire younger age group (24.3% vs 8.9%). Age therefore is a significant independent prognostic factor even when the "good risk" older patients are compared with younger patients.

The high mortality rate from an acute MI in

Table IV Mortality risk related to electrocardiographic site of infarction and various complications occurring during the hospital course

| Complication | Survivors | Non survivors | % prevalence in study group | % mortality | p value |
|------------------------|-----------|---------------|-----------------------------|-------------|---------|
| Site of MI | | | | | |
| Anterior | 72 | 35 | 61.1 | 3.7 | |
| Inferior | 37 | 16 | 30.3 | 30.2 | |
| Unknown | 10 | 5 | 8.6 | 33.3 | |
| Shock | 6 | 24 | 17.1 | 80 | 0.001 |
| Pulmonary edema on CXR | 10 | 24 | 14.3 | 60 | 0.01 |
| CHF | 64 | 42 | 60.6 | 33.6 | 0.01 |
| Complete heart block | | | | | |
| Anterior | 0 | 5 | | | |
| Inferior | 1 | 2 | 5.1 | 88.9 | 0.001 |
| Unknown | 0 | 1 | | | |
| LBBS | | | | | |
| Admission ECG | 7 | 3 | 5.7 | 30.0 | |
| Developed in hospital | | 1 | 0.5 | 100 | 0.28 |
| RBBS | | | | | |
| Admission ECG | 5 | 3 | 4.6 | 37.5 | |
| Developed in hospital | | 0 | 1.1 | 100 | |
| Total | 119 | 56 | | | |

MI = myocardial infarction CXR = chest x-ray CHF = congestive heart failure ECG = electrocardiogram LBBS = left bundle branch block RBBS = right bundle branch block

Per cent mortality calculated by formula $\frac{N \text{ of non survivors}}{\text{No. of non survivors} + \text{survivors}}$

Other studies however have shown an increased mortality rate associated with complete heart block and BBB whether present prior to an acute MI or developing in association with an acute MI.^{1,2}

Cardiogenic shock was the major cause of death in this series of hospitalized patients. The electrocardiographic location of the MI did not influence mortality rate since anterior and inferior MIs were associated with similar mortality rates (32.7% and 30.2% respectively Table IV). Pump failure (shock + CHF) was the major cause of death in patients with anterior and inferior MIs (Table V). A larger percentage of patients with anterior MIs (16.8%) compared to inferior MIs (9.4%) died from pump failure. Anterior MIs potentially result in the loss of a larger mass of myocardium than do inferior MIs and are often associated with more severe myocardial dysfunction.³

Inferior MIs occurred in 53 patients and were associated with shock in four patients (Table V). In three of these four patients papillary muscle dysfunction probably contributed to the shock. In the fourth patient the inferior MI was associated with a prior anterior MI. Isolated inferior MIs without prior anterior MIs and without

papillary muscle dysfunction were not associated with shock.

The second most common cause of death was external cardiac rupture (17.9% Table V). The incidence of autopsy documented cardiac rupture was 17.9% (10 of 56) in this study in which the autopsy rate was 41% (23 of 56). An additional two patients suffered a ruptured ventricular septum and died postoperatively. The inclusion of these two patients brings the total incidence of cardiac rupture causing death to 20.7%. Cardiac rupture may have occurred in an additional four patients in whom the clinical signs of cardiac rupture—sudden chest pain and or unconsciousness which is associated with apnea, absent peripheral pulses, an unobtainable blood pressure and the rapid development of a sinus or junctional bradycardia—were observed but autopsy confirmation was not obtained (Table V).² When these four patients are added to the ten patients with autopsy documented cardiac rupture and the two patients with a ruptured ventricular septum the incidence of cardiac rupture in this series becomes 28.6%. This is over two and one half times the incidence of cardiac rupture reported in most series and suggests that the elderly dying of acute MI have a higher incidence

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the elderly may be related to the high incidence of coexisting pathological processes which could contribute to pump failure.³⁷⁻³⁹ Pathological changes occurring with aging include myocardial fibrosis, aortic and mitral valve degenerative changes and calcification, senile cardiac amyloidosis and presbycardia.³⁷⁻³⁹ The high incidence of myocardial rupture in the elderly may also be a result of the chronic pathological changes that affect the aged myocardium. In this sense, advanced age is indeed a potent nonmodifiable risk factor that is associated with a high mortality rate.³⁹

Summary

The history and clinical course of 175 patients aged 70 and older (Group A) with acute myocardial infarction (MI) was studied to determine the hospital mortality rate in this population group and to determine the clinical factors that influenced the hospital mortality rate. The mortality rate of a second group of 772 patients below age 70 years (Group B) admitted during the same time period was determined for comparison with the mortality rate in Group A.

The hospital mortality rate in Group A (32%) was 3.9 times the hospital mortality rate in Group B (8.2%). Advanced age was associated with a significantly higher mortality rate even when so-called good risk patients from Group A were compared with patients in Group B.

The major causes of death in this hospitalized group of patients aged 70 and older were shock (33.9%) and cardiac rupture (28.6%). Factors that significantly influenced hospital mortality rate in the elderly group were the development of shock, pulmonary edema on chest x-ray, a clinical diagnosis of congestive heart failure and the development of complete heart block or new bundle branch block during the hospital course.

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Table I Age and sex in 15 patients

| | N | Age (yrs) | Mean (yrs) | SD |
|---------|----|--------------|---------------|------|
| Total | 15 | 35-72 | 53.5 | 10.3 |
| Males | 8 | 41-72 | 55.0 | — |
| Females | 7 | 35-66 | 51.9 | — |

Table II Plasma volume variations

| | Pre injection | 2 min post injection | 30 min post injection |
|------|---------------|-------------------------|--------------------------|
| Mean | 2903 ml | 3384 ml | 3005 ml |
| SD | 720 | 792 | 366 |
| P< | 0.001 | | 0.001 |
| | NS | | |

for capillary fluid exchanges calculated as COP-LVEDP is observed (Table IV) decreasing from a mean 8.4 mm Hg to a slightly negative gradient of -0.8 mm Hg. Forty four per cent of this shift in gradient is accounted by the changes in COP (3.8 of 8.7 mm Hg).

Discussion

It is well recognized that an intravascular bolus injection of contrast media may precipitate acute pulmonary edema.¹⁻³ The observed expansion in plasma volume at two minutes after injection is consistent with other similar studies^{2,3} and represents an acute plasma expansion of 8 to 10 ml for each milliliter of hyperosmolar solution injected.

The LVEDP elevation is well recognized as a major cause of pulmonary edema.¹⁰⁻¹² Almost a century ago Starling² suggested that intravascular colloids promote fluid absorption from the interstitial space at the microcirculatory level. Guyton and associates¹ and other workers^{22,23} subsequently presented quantitative evidence to substantiate the importance of the relation between left atrial pressure and plasma protein concentration on the development of pulmonary edema. Since the more extensive availability of instruments for clinical measurement of COP, the clinical importance of oncotic pressure in the evolution of pulmonary edema has been better defined.¹⁴ Stein and co-workers^{2,23} presented evi-

dence for pulmonary edema formation in the absence of left ventricular failure if the oncotic pressure is significantly decreased. Da Luz and associates¹² showed that pulmonary edema may appear in the absence of a significant increase of the left ventricular filling pressure after acute myocardial infarction if the oncotic pressure is significantly decreased leading to an almost abolished gradient for capillary fluid exchanges. In the critically ill patient the gradient for capillary fluid exchanges represents a much better predictor of pulmonary edema than the isolated measurement of LVEDP, an abolished gradient representing a major risk of pulmonary edema whatever the LVEDP.^{10,11,23} The hemodilution hypervolemia induced by a bolus injection of contrast media increases the LVEDP and simultaneously decreases the COP level. Those changes invert (positive to negative) the gradient for capillary fluid exchanges resulting in a pulmonary edema prone situation. It should be noted however that the relative importance of the decrease in COP and the increase in LVEDP varies from patient to patient in relation to the magnitude of the LVEDP changes. The variations in COP are relatively fixed and determined by the volume changes.

We conclude from this study that after a bolus injection of contrast media the total intravascular pressure changes predisposing to pulmonary edema are almost equally shared by the hydrostatic and oncotic pressure changes. These findings further clarify the mechanism of pulmonary edema induced by contrast media.

Summary

Angiographic contrast media are known to induce alterations in cardiovascular dynamics which may result in acute pulmonary edema. The risk of pulmonary edema was previously shown to be negatively correlated to the level of colloid oncotic pressure (COP). It was also shown that the gradient between COP and left ventricular end diastolic pressure (LVEDP) represents a better predictor of pulmonary edema than does LVEDP alone. The present report evaluates the effects of a bolus injection of contrast media on those pressures as predisposing factors for pulmonary edema.

Our data are based on 15 unselected patients admitted for coronary angiography. The plasma volume increased by 16.5% (2903 to 3384 ml) and

Effects of angiographic contrast media on colloid oncotic pressure

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Left ventriculography requires a rapid injection of hyperosmolar contrast material into the arterial side. These agents are known to decrease myocardial contractility^{1,2} and cause a rapid increase in blood volume and cardiac output. The general risk of pulmonary edema is 0.08% in all angiographic procedures.^{3,4} This risk may be significantly higher in patients with a compromised ventricular function.^{5,6} The problem of pulmonary edema has been attributed to an increased circulating blood volume and filling pressure. The importance of acute hypervolemia on the oncotic pressure of plasma and edema formation even if suspected remains to be evaluated and quantified. It is recognized that COP is inversely correlated to the risk of pulmonary edema.⁷ Also it has been demonstrated that the risk of pulmonary edema is better predicted by the gradient for capillary fluid exchanges represented by the difference between colloid oncotic pressure (COP) and left ventricular end diastolic pressure (LVEDP) than by LVEDP alone. In the present study the effects of a bolus injection of contrast media on COP and on the COP/LVEDP gradient are examined.

Material and methods

The group consisted of 15 unselected patients admitted for elective coronary angiography. It included eight males and seven females with a

mean age of 53.5 years (Table I). The patients were studied in the fasting state and received 10 mg diazepam orally as premedication. From 40 to 60 ml of meglumine diatrizoate (Renographin 76%) was injected in 2.5 to 4 seconds for the left ventricular angiogram.

A single injection of radioiodinated human serum albumin (R1¹²⁵I-SA) was used for determination of the three sequential plasma volumes. They were measured before, at two and at 30 minutes following the injection of contrast material.

COP was measured on plasma by the use of a transducer membrane system representing a modification of the technique of Prather¹⁸ Weil¹⁹ and their colleagues. Arterial blood was obtained at the same time as plasma volume sampling.

Results

The sequential changes in plasma volume following injection of contrast media are summarized in Table II. A 16.5% increase in plasma volume is observed at two minutes. A return towards normal values is found at 30 minutes although a slight non significant elevation still remains compared to the baseline.

The COP response is shown in Table III. Contrasting the increase in plasma volume, a significant fall in plasma COP (16.2%, $P < 0.001$) is observed. In 30 minutes the COP has returned to the control level.

The end diastolic pressure significantly increases (Table III) at two minutes in parallel with the changes in plasma volume.

A significant shift ($P < 0.001$) of the gradient

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Table III COP and LVEDP (mm Hg) responses after contrast ventriculography

| Case | Colloud oncotic pressure | | | LVEDP | |
|---------------|--|----------------|----------------|--|----------------|
| | Pre | 2 min | 30 min | Pre | 2 min |
| 1 | 26.1 | 23.0 | 24.6 | 12 | 15 |
| 2 | 24.8 | 20.1 | 23.2 | 14 | 20 |
| 3 | 23.8 | 18.6 | 22.2 | 12 | 15 |
| 4 | 22.4 | 19.8 | 25.1 | 10 | 17 |
| 5 | 24.3 | 20.9 | 21.6 | 15 | 20 |
| 6 | 24.7 | 21.4 | 24.1 | 15 | 15 |
| 7 | 23.0 | 20.4 | 25.0 | 22 | 25 |
| 8 | 22.4 | 19.4 | 22.5 | 15 | 22 |
| 9 | 20.8 | 17.5 | 20.4 | 8 | 15 |
| 10 | 22.8 | 20.0 | 21.0 | 10 | 18 |
| 11 | 28.3 | 23.8 | 22.9 | 17 | 20 |
| 12 | 24.7 | 19.3 | 22.7 | 16 | 30 |
| 13 | 23.8 | 17.2 | 21.8 | 10 | 15 |
| 14 | 17.9 | 14.5 | 16.4 | 33 | 33 |
| 15 | 20.9 | 17.5 | 20.1 | 17 | 18 |
| Mean \pm SD | 23.4 \pm 2.4 | 19.6 \pm 2.3 | 22.7 \pm 2.6 | 15.1 \pm 5.9 | 19.9 \pm 5.4 |
| P | <div style="display: flex; justify-content: space-around; align-items: center;"><div style="border-top: 1px solid black; width: 150px; text-align: center;">< 0.001</div><div style="border-top: 1px solid black; width: 150px; text-align: center;">< 0.001</div></div> | | | <div style="border-top: 1px solid black; width: 200px; text-align: center;">< 0.001</div> | |
| | NS | | | | |

two minutes after injection of a 50 c.c. bolus of meglumine diatrizoate (Renographyn 76%) and had returned towards normal at 30 minutes. In parallel the COP decreased from 23.4 ± 2.4 to 19.6 ± 2.3 mm Hg ($P < 0.001$) to return the 22.7 ± 2.6 . The COP LVEDP gradient decreased by 8.7 mm Hg (8.4 to -0.3 $P < 0.001$). Such a gradient was well within the danger zone of pulmonary edema. These findings further clarify the mechanisms of pulmonary edema induced by contrast media.

Table IV COP LVEDP gradient changes (mm Hg)

| | COP LVEDP changes | | COP changes |
|------|-------------------|----------------------|---|
| | Pre injection | 2 min post injection | Pre injection -2 min post injection |
| Mean | 8.4 | -0.3 | -3.8 |
| SEM | 1.9 | 1.8 | 0.3 |
| P < | 0.001 | | |

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Fig 1 Lymphangiogram of left ventricle from normal dog

Table 1 Percentage of left ventricular surface area occupied by lymphatic vessels: data obtained by grid and point counts

| Protocol | N | Mean point count | SEM | Surface area (%) | P (diff from normal) |
|--------------------------------------|---|------------------|------|------------------|----------------------|
| Normal dog left ventricle | 6 | 164 | 0.11 | 66% | |
| Coronary occlusion—ischemic zone | 7 | 90 | 0.06 | 36% | < 0.001 |
| Coronary occlusion—noninfarcted zone | 7 | 281 | 0.22 | 112% | < 0.001 |
| Hyaluronidase—normal dog | 8 | 345 | 0.18 | 138% | < 0.001 |
| Hyaluronidase—infarcted zone | 7 | 522 | 0.34 | 209% | < 0.001 |
| Hyaluronidase—noninfarcted zone | 7 | 265 | 0.08 | 106% | < 0.001 |
| Bioassay of toxic lymph | 5 | 48 | 0.21 | 17% | < 0.001 |
| Spontaneous arrhythmias | 3 | 119 | 0.11 | 4.8% | NS |

fivefold magnification using a 0.1 mm focal spot Siemens tube and exposure factors of 50 kV 0.01 sec and 30 mA. With this technique it was possible to visualize 50 to 80 micron lymphatic vessels.

2 Hyaluronidase administration In six normal dogs and in seven dogs beginning 20 minutes prior to coronary occlusion hyaluronidase (Sigma Chemical St. Louis, Mo.) was administered

intravenously in a dose of 500 IU every 6 hours for a total of four or five doses.

3 Cardiac lymph collection In five live dogs the chest was opened through a left thoracotomy incision in the third intercostal space and the pericardium was incised parallel to the phrenic nerve. Evans Blue (0.5 ml) was injected subendocardially at the left ventricular apex to allow visualization of the lymphatics. The main cardiac

Cardiac lymph and lymphatics in normal and infarcted myocardium

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Despite sporadic interest in the lymphatic drainage of the myocardium the possibility that disordered lymphatic function contributes to tissue destruction following coronary artery occlusion has not been systematically examined. During a study on the normal coronary lymphatic drainage we found that hyaluronidase had a striking influence on lymphatic visualization in the heart.¹ Because hyaluronidase also has a clear influence on the evolution of myocardial necrosis after coronary occlusion,^{2,3} and because an unequivocal explanation for the mechanism by which hyaluronidase induces the salutary response is not available we undertook a systematic investigation into the lymphatic drainage of normal and infarcted myocardium and the impact of hyaluronidase on both. The results are consistent with an important role of altered lymphatic drainage in the evolution of myocardial infarction and with a mechanism of hyaluronidase action which includes better sustained lymphatic drainage following myocardial infarction perhaps facilitating removal of high molecular weight toxic substances such as lysosomes from the ischemic myocardium.

Methods and materials

Studies were performed in 48 mongrel dogs of either gender weighing about 20 kilograms. Anes-

thesia was induced and maintained with sodium pentobarbital (30 mg/kg) and ventilation was maintained through an endotracheal tube with a Harvard respirator which provided 200 to 300 cc of room air/breath at a rate of 18 to 20/minute.

Catheters were placed in the aorta from the right femoral artery for blood pressure monitoring and in the inferior vena cava from the right femoral vein for maintaining anesthesia. In experiments during which the coronary artery was occluded without thoracotomy an additional catheter was placed via the left femoral artery in a superselective position in the left anterior descending or left circumflex coronary artery. Coronary occlusion was accomplished in this way to avoid the possibility of venous or lymphatic obstruction which may occur when ligation is the method used to occlude the coronary arteries. The artery was occluded with either a piece of Gelfoam (5 x 1 mm) or the tip of radiopaque polyethylene catheter using a modification of a technique described from this laboratory by Cohen and Eldh.⁴ All animals were killed at 24 hours and cardiac lymphangiography was performed immediately after death.

1 Technique for cardiac lymphangiography
Lymphatic vessels in the apical portion of the left ventricle were cannulated postmortem with a 30 gauge Becton Dickinson lymphangiography set using a 2.5 magnification lens. The contrast agent utilized was made by adding 30 grams of barium sulfate to 3 to 5 ml of Iodamide 420 (Bracco Milan, Italy). Five drops of food coloring were added to allow different colors for each lymphatic vessel. The contrast agent was injected under gentle manual pressure until the lymphatic vessels were filled. The heart was x-rayed with

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Fig 3 Lymphangiogram from dog pretreated with hyaluronidase. Coronary arteries were patent in the dog.

cm served as a single basic unit as it corresponded to 1 cm of ventricular myocardium (fivefold magnification was used for filming the lymphangiogram). Because of the 1 cm separation between the lines 25 crossings were present in each basic unit. Each 1 cm on the grid corresponded to 2 mm of the ventricular myocardium. A point was counted whenever a crossing coincided with a visualized lymph vessel in the lymphangiogram. This approach provides not a count of lymphatic vessels but rather an index of their volume relative to that of ventricular myocardium. The entire left ventricular surface was evaluated whenever point counts were obtained. Following coronary occlusion the entire infarcted or noninfarcted zones were counted.

Mean values have been presented with the standard error of the mean as the index of dispersion. Statistical analyses were performed where appropriate with the Student *t* test. The null hypothesis was rejected when *P* was less than 0.05.

Results

1 Effect of coronary occlusion on lymphangiograms. A typical normal myocardial lymphangiogram is shown in Fig 1. In the normal myocardium there was 34 ± 0.11 points/cm² ventricle

equivalent to 6.6% of the ventricular area (Table I). The variation from animal to animal was small as evidenced by a coefficient of variation of only 16.4%.

Acute coronary occlusion induced striking statistically significant changes in the visualization of lymphatics on lymphangiography in both the infarcted zone and in the surrounding noninfarcted tissues. In the infarcted zone (Fig 2, Table I) there was a marked reduction in the number of lymphatics visualized (0.90 ± 0.06 points/cm² ventricle, 3.6% of ventricular area, $p < 0.001$ vs normal). Conversely the noninfarcted zone showed a considerable increase in lymphatic visualization (2.81 ± 0.22 points/cm² ventricle, 11.2% of ventricular area, $p < 0.001$ vs normal).

2 Effect of hyaluronidase on lymphangiograms. Hyaluronidase augmented myocardial lymphatic visualization in the normal dog. In six normal dogs lymphatic density following hyaluronidase pretreatment was increased significantly (3.45 ± 0.18 , 13.8% of ventricular area, $p < 0.001$ vs untreated normal myocardium) (Fig 3).

Hyaluronidase pretreatment resulted in improved visualization of lymphatics in the infarcted zones (0.22 ± 0.34 points/cm² ventricle, 20.9% of ventricular area, $p < 0.001$ vs



Fig 2 Lymphangiogram from dog with myocardial infarction following coronary occlusion. The arrows indicate the ischemic zone.

lymphatic trunk which measures approximately 1.5 mm in diameter was cannulated 2 to 3 cm above the left atrial appendage just before it enters the cardiac lymph node. The catheterization was accomplished with an angiograph catheter (Intercath 22 gauge size Deseret Co Sandy Utah) after ligation of the lymphatic trunk to engorge the vessel.

Lymph was collected in open tubes during free flow or with slight negative pressure for 2 hours prior to coronary occlusion and in 2 hour collections for 4 to 8 hours following coronary occlusion. Samples were collected on ice spun to remove visible blood cells and were frozen immediately for bioassay the following day in four of the five experiments. In the remaining experiment the lymph was bioassayed immediately after the collection on ice.

4 Bioassay of myocardial lymph The lymph samples were assayed in five normal dogs. The left coronary artery was catheterized as described above the blood pressure and the ECG were continuously monitored.

First the effect on the electrocardiogram of 1.0 ml of normal saline injected into the left coronary artery of normal animals was evaluated for 10 minutes as a control. As a second control

lymph collected prior to coronary occlusion was injected as a 1.0 ml bolus and blood pressure and the electrocardiogram were monitored for 60 to 120 minutes. Lymph obtained during the first 2 hours following coronary occlusion was then injected into the coronary artery of normal stable dogs and the animals were observed for 60 to 120 minutes. Finally lymph collected during the second 2 hour interval following coronary occlusion was injected into the coronary artery of normal stable dogs and the animals were observed for an additional 4 to 6 hours.

Following termination of the experiment lymphangiograms were obtained in all animals.

In an additional three normal dogs with cardiac arrhythmias induced by placement of an electromagnetic flow meter probe around the coronary artery but in which no injections of any agent into the coronary artery were performed lymphangiograms were obtained to assess the contribution of arrhythmias to lymphangiographic features.

5 Methods of analysis A grid was prepared to serve as an overlay on the fivefold magnified lymphangiograms allowing quantification of visualized lymphatics. The grid consisted of lines drawn at right angles 1 cm apart. Each 5 × 5



Fig 5 ECG changes in a normal dog following injection of saline (a) normal myocardial lymph (b) lymph obtained during the first 2 hours following coronary occlusion (c) and lymph obtained during the second 9 hour interval following coronary occlusion (d)

occlusion. The better sustained lymphatic system may be a cause or a consequence of favorable hyaluronidase influence on the course of tissue destruction. If it were causal, it might be assumed that the preserved lymphatics drain toxic material from the affected myocardium following coronary occlusion. Our fourth observation is that indeed a factor toxic to the heart is found in lymph draining the myocardium following coronary occlusion.

These observations permit three major lines of investigation to be integrated into a single conceptual framework. An elegant series of studies has already implicated membrane damage and lysosomal enzyme release as participants in the development of tissue necrosis with ischemia.¹⁻⁴ A second line of investigation has provided unequivocal evidence that hyaluronidase reduces myocardial necrosis following coronary occlusion but with no clear indication as to what the protective mechanism may be.^{2,12,13} Studies on lymphatic drainage from the hypoxic or ischemic heart have indicated that quantitatively important changes in lymph flow occur and that obstruction of lymphatic outflow has a pernicious influence on the course of myocardial necrosis but have a contribution to define their overall role in the evolution of myocardial infarction.¹⁴ The working hypothesis is that

lymphatic drainage is a determinant of tissue survival after coronary occlusion because toxic products, possibly the products of damaged myocardial cells, are removed via this route.

What species of molecule is most likely to be drained primarily by lymphatics? For molecules of a size too large to allow easy access to the bloodstream via the blood capillary wall, an important avenue of escape is likely to occur via the lymphatics. Consistent with this concept, three studies have demonstrated that enzymes such as creatine phosphokinase appear in myocardial lymph well before their concentration in blood rises following coronary occlusion.¹⁵⁻¹⁷

Attention has been focused primarily on membrane disruption and evidence that lysosomal enzyme release occurs when the membranes become abnormal with considerably less attention paid to the role of the enzymes once they are released. Certainly their local concentration and thus their toxicity must depend not only on their rate of release but also on the rate at which they are degraded or carried away. Thus the transport and behavior of the enzymes and the components involved in their transport such as the interstitial space, lymphatic vessels, or coronary venous blood must also be considered. Viewed in the perspective of our lymphangiograms following coronary occlusion, perhaps it is not surpris-



Fig 4 Lymphangiogram obtained from dog pretreated with hyaluronidase and then subjected to coronary occlusion. The arrows indicate the ischemic zone.

untreated infarction) (Fig 4). There was no difference in the lymphatic density in the non-infarcted zone in hyaluronidase pretreated and untreated dogs with coronary occlusion (2.65 ± 0.08 vs 2.81 ± 0.22).

3 Effect of cardiac lymph injections into the coronary arteries. Saline and normal lymph injected into the coronary arteries induced no electrocardiographic changes (Figs 5A and 5B). Lymph collected during the first two hours following coronary occlusion induced relatively minor and transient electrocardiographic changes (Fig 5C). Lymph collected 2 to 4 hours following coronary occlusion induced in each case malignant arrhythmias in the normal dogs (Fig 5D). In all cases the arrhythmias were delayed in onset, first becoming evident in 10 to 15 minutes following injection and becoming progressively more severe. Multifocal ventricular premature contractions were followed by ventricular tachycardia and ventricular fibrillation within 30 to 90 minutes following injection in three of the five dogs. In the other dogs used for bioassay, prolonged bouts of ventricular tachycardia subsequently reverted to normal rhythm with ST segment elevation > 8 mm at 6 hours following the injection of toxic lymph when the experiment was terminated.

Lymphangiography demonstrated an increase in the number and size of visualized lymphatics present in each of the five dog hearts which had received toxic lymph injections into the coronary artery (4.3 ± 0.27 points/cm² ventricle 17.2% of ventricular area $p < 0.001$ vs normal) (Fig 6). No significant increase in lymphatic density could be detected in the three dogs with cardiac arrhythmias induced by mechanical stimulation (1.19 ± 0.11 points/cm² ventricle 4.8% ventricular area $p = NS$).

Discussion

There are four new and probably related observations in this study which may shed light on the pathogenesis of progressive tissue destruction following coronary artery occlusion. First, a remarkable reduction in visualized lymphatic channels from ischemic myocardium occurs within 24 hours of coronary occlusion, well before the disappearance of lymphatic vessels can be accounted for on the basis of coagulation necrosis. Second, hyaluronidase has a striking influence on the lymphatic vascular tree of the normal heart. Third, sustained integrity of the myocardial lymphatic system parallels the reduction in myocardial tissue destruction associated with hyaluronidase administered prior to acute coronary

necrosis one might anticipate substantial release of potassium and other small ions or organic moieties along with the intracellular protein release. Detailed studies on the character of lymph draining the ischemic heart²⁷ and kidney²⁸ have detected little or no change in potassium or protein concentration. The simplest explanation would appear to be that blood flow in the ischemic zones while markedly reduced, is still adequate to wash away the small molecules which easily diffuse into capillaries. Whatever the explanation potassium and other small ions are not likely candidates as the toxic factor.

The role of lymphatics in the evolution of tissue necrosis following coronary occlusion in the protective effect of hyaluronidase and in the clearance of toxic factors from ischemic myocardium clearly requires more detailed evaluation. Perhaps the highest priority should be placed on identifying and characterizing the toxic material or materials a task which should be facilitated by what is clearly a very high concentration in the draining lymph. As little as 0.5 ml injected into a healthy dog's coronary artery was lethal.

Summary

Cardiac lymphangiography was applied to 29 normal dogs (ND) and 14 dogs following acute coronary occlusions. In five of the ND lymph collected from infarcted dogs was selectively injected into the coronary artery prior to the lymphangiogram. In ND the lymphatic density (LD) was 6.6% ventricular area (VA).

Acute coronary occlusion induced a change in the LD. The infarcted zone registered a decrease in LD (3.6% of VA $p < 0.001$ vs ND). Hyaluronidase increased LD in normal dogs (13.8% of VA $p < 0.01$ vs ND). Hyaluronidase pretreatment increased the LD in infarcted myocardium (20.9% of VA $p < 0.001$ vs non treated infarcts). No difference was seen between uninfarcted areas of treated and nontreated animals (10.6% vs 11.2% of VA). Lymph was collected from cardiac lymphatics in five dogs before and after coronary occlusion. When selectively injected into coronary arteries of ND post infarct lymph induced ECG changes of ischemia, arrhythmias and increased the LD (14.6% VA $p < 0.001$ vs ND). The results suggest (1) Cardiac lymphatics are altered in the uninfarcted and infarcted zones following coronary occlusion. (2) Hyaluronidase preserves the lymphatic density in infarction. (3)

Lymph collected from zones of infarction is toxic.

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Fig 6 Lymphangiogram of left ventricle in a normal dog following the introduction of toxic lymph into the coronary artery

ing that lysosomal enzyme content of lymph following coronary occlusion was increased but that the increase was disappointingly modest. An unstated premise in such studies is that the interstitium of the infarcting zone communicates freely with the draining lymphatic trunks—a premise which now seems unlikely.

How does hyaluronidase act to modify myocardial infarction? A number of suggestions including reduction of interstitial edema, facilitation of perfusion via collateral blood flow, and enhanced delivery of critical substrates through the interstitium have been made.

Among the suggestions made, the possibility that hyaluronidase might exert its salutary effect at least in part by increasing the washout of toxic metabolites has been raised, but no direct evidence concerning this possibility was offered. Some insight may be gained through close examination of the specific actions of hyaluronidase and the normal physiology of its substrate. Hyaluronic acid is a viscous hydrophilic mucopolysaccharide of the connective tissue ground substance which holds the cells in its jelly-like matrix by its viscosity. In model systems of isolated proteoglycans, the polysaccharide network has a negligible

effect on the distribution and diffusion of oxygen, water, and sugars. At physiological hyaluronic acid concentrations there is, however, measurable retardation in the diffusion of molecules as large as plasma proteins, presumably because of steric restriction. Hyaluronidase apparently facilitates diffusion of large molecules by enhancing the probability that a particle finds a path in the network through which it can move.

From this analysis, the possibility that hyaluronidase influences myocardial infarction by facilitating the delivery of small molecular weight substrates or oxygen seems less likely than that the diffusion of larger molecules such as protein is influenced critically. Consistent with that action, hyaluronidase has been documented as increasing lymphatic flow after intravenous injection in the dog.³

What is the toxic substance likely to be? Because of normal lymphatic function, toxic proteins, perhaps lysosomal enzymes, are likely candidates. No direct evidence from this study is as yet available because it was necessary to utilize all of the small volumes of lymph collected for the bioassay to toxicity. With the well-documented disruption of cell membranes which occurs during

Effects of circulatory arrest and rewarming on regional blood flow during surface-induced hypothermia

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Although intensive research efforts have clarified many aspects of hypothermic physiology the distribution of regional blood flow has remained obscure. However the relatively recent development of a technology based on the use of nonre-circulating radioactive microspheres has made it possible to simultaneously determine regional blood flow throughout the body. In a previous communication¹ we reported on the changes in distribution of cardiac output regional blood flow and vascular resistance during the cooling phase of a method of deep surface induced hypothermia described in our laboratory and used as an adjunct for the correction of congenital cardiac defects in infants.²⁻⁴ This report is intended to demonstrate the effects of induced circulatory arrest on regional blood flow and blood flow distribution during the rewarming phase of surface hypothermia.

Materials and method

A detailed description of the operative procedure microsphere administration and radionuclide counting techniques has been provided in our previous report. In summary catheters were inserted into the inferior vena cava abdominal aorta and left ventricle of 4 to 7 kg monkeys

(*Macaca mulatta*) three days prior to the study. On the day of the experiment control (awake) determinations were done. Then the animals were anesthetized and surface cooled by our method^{1,2} which includes the use of deep ether anesthesia in 100% O₂, artificial ventilation maintained at normal levels for normothermia so as to gradually induce respiratory alkalosis during cooling and the administration of 10 cc/kg low molecular weight dextran (10% in DW) between 35° and 25° C during cooling.

Five animals were cooled to 20° C rectal temperature maintained for 30 minutes and rewarmed by floating the animal on a plastic sheet over warm water (40° C). Another group of four animals were similarly cooled opened by sternotomy and a 30 minute period of circulatory occlusion was induced by crossclamping the caudal pulmonary artery and aorta. Cardioplegia was accomplished by injecting 10 cc of Young's Solution* proximal to the aortic crossclamp. Resuscitation was accomplished by manual cardiac massage and the administration of 300 mg of calcium chloride to neutralize the Young's Solution. Defibrillation when necessary was by 50 volt AC electroshock. Rewarming was started at the time of massage.

At the end of each experiment the animal was exsanguinated and the major organs were removed weighed and placed in plastic vials for measurement of radioactivity. The remainder of

Young's Solution contains 0.81 gm of potassium citrate 2.45 gm of magnesium sulfate 0.001 gm of neostigmine methyl sulfate and sufficient water to make 100 ml. pH is adjusted to 7.4 with NaHCO₃.

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Table 1 Systemic hemodynamic parameters and blood gases*

| | | Unanesthetized control 37° C | Rewarming ether anesthesia | | | |
|--------------------------|----|------------------------------------|-------------------------------|-------------|-------------|-------------|
| | | | 20° C | 25° C | 30° C | 37° C |
| HR (beats/min) | NA | 184 ± 8 | 56 ± 5 | 107 ± 7 | 139 ± 7 | 185 ± 12 |
| | A | 173 ± 3 | 60 ± 4 | 112 ± 6 | 163 ± 6† | 193 ± 8 |
| MAP (torr) | NA | 120 ± 4 | 28 ± 1 | 48 ± 4 | 58 ± 3 | 65 ± 3 |
| | A | 133 ± 8 | 30 ± 3 † | 75 ± 8 † | 82 ± 6 ‡ | 73 ± 1 |
| CO (mL/min /kg) | NA | 242 ± 36 | 63 ± 11 | 146 ± 23 | 179 ± 22 | 205 ± 19 |
| | A | 278 ± 46 | 86 ± 8 | 145 ± 18 | 223 ± 30 | 118 ± 38 |
| SV (mL/kg) | NA | 1.30 ± 0.17 | 1.15 ± 0.25 | 1.40 ± 0.25 | 1.31 ± 0.20 | 1.11 ± 0.0* |
| | A | 1.62 ± 0.30 | 1.45 ± 0.11 | 1.36 ± 0.17 | 1.38 ± 0.20 | 0.97 ± 0.15 |
| TVR (torr/ L/min.) | NA | 115 ± 10 | 61 ± 8 | 50 ± 4 | 50 ± 4 | 50 ± 5 |
| | A | 77 ± 5 | 50 ± 3 | 81 ± 8† | 59 ± 4 | 67 ± 2† |
| pH | NA | 7.48 ± 0.01 | 7.80 ± 0.08 | 7.64 ± 0.06 | 7.58 ± 0.04 | 7.40 ± 0.04 |
| | A | 7.51 ± 0.03 | 7.60 ± 0.08 | 7.57 ± 0.06 | 7.47 ± 0.08 | 7.32 ± 0.04 |
| PaO ₂ (torr) | NA | 113 ± 7 | 475 ± 28 | 409 ± 15 | 401 ± 20 | 371 ± 49 |
| | A | 105 ± 5 | 281 ± 79† | 286 ± 78 | 228 ± 83 | 207 ± 79 |
| PaCO ₂ (torr) | NA | 31 ± 2 | 11 ± 1 | 12 ± 1 | 14 ± 2 | 23 ± 9 |
| | A | 33 ± 1 | 22 ± 4 † | 22 ± 4† | 25 ± 4† | 36 ± 5† |
| Hematocrit (%) | NA | 36 ± 3 | 25 ± 3 | 27 ± 3 | 28 ± 3 | 31 ± 9 |
| | A | 37 ± 2 | 28 ± 1 | 32 ± 1 | 33 ± 3 | 30 ± 2 |

*The values are means and standard errors of the means from five non arrested (NA) and four arrested (A) monkeys. and † denote $p \leq 0.05$ and ‡ denote $p \leq 0.01$ and § denote $p \leq 0.001$. The statistical significances are shown in asterisks () when the results are compared to that of unanesthetized control values by paired t test. The statistical significances are shown in daggers (†) when the results are compared between NA and A values by Student's t test. HR = heart rate MAP = mean arterial pressure CO = cardiac output SV = stroke volume TVR = total vascular resistance

(MAP) was significantly below control through out rewarming in both groups however the MAP of arrested animals was significantly greater than non arrested animals at 20° 25° and 30° C Cardiac output in both groups was 30% of control at 20° C In the non arrested animals cardiac output increased steadily with rewarming to values not significantly different from control at 37° C Arrested animals displayed a similar trend until 30° C at 37° C output decreased slightly and was significantly below control In both groups stroke volume was not significantly different from control except for a decrease in the arrested group at the completion of rewarming (37° C)

Total vascular and organ resistance (Table 1 Fig 1) Total vascular resistance (TVR) was insignificantly reduced when compared to the control value in the non arrested group at 20° C during rewarming A decline to a significant degree was noted at 25° C that was maintained

through the completion of rewarming The TVR of arrested animals was significantly reduced at 20° C following resuscitation but resistance increased to near control at 25° C declined again significantly at 30° C and was rising at the completion of rewarming (37° C) When the two groups were compared arrested animals had significantly higher TVR at 25° and 37° C

Cerebral vascular resistance was slightly greater than control at 20° C in non arrested animals but declined steadily during rewarming and a significant reduction to 65% of control was noted at the completion of rewarming The cerebral vascular resistance of arrested animals was considerably less at 20° C than in non arrested counterparts (75% vs 120% of control values) although the difference was not significant due to individual variation During rewarming cerebral vascular resistance in the arrested group increased with temperature until 30° C and decreased slightly thereafter

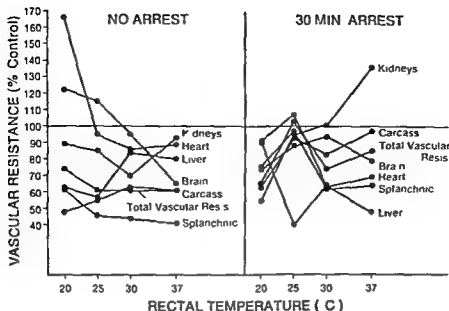


Fig 1 Total vascular and organ resistances plotted with the unanesthetized normothermic control value (not shown) as the 100% value

the body was ashed and a 20% aliquot of the mixed ash was also placed in vials for counting

Data collection and analysis Arterial central venous and left ventricular pressures and ECG (Lead II) were continuously recorded on a Hewlett-Packard model 7788A recorder with appropriate amplifiers Cardiac outputs were determined in duplicate by the dye dilution technique Immediately after each cardiac output determination and microsphere injection arterial blood samples were analyzed with a Radiometer Model 27 blood gas analyzer Temperatures of the pH and blood gas electrodes were preadjusted to sampling temperature in order to eliminate temperature correction errors

The distribution of blood flow was determined by left ventricular injections of ^{45}Sc ^{90}Nb ^{86}Sr ^{51}Cr and ^{141}Ce nuclide labeled microspheres By using one isotope at each data collection point five separate blood flow determinations were done in each animal

The radioactivity of each vial containing tissue or ash was counted using a Packard NaI Model 9011 scintillation counter energy distribution patterns were recorded on a Packard Pulse Height analyzer and the composite spectra for all five nuclides were stored on magnetic tape for processing by a PDP 15 computer

The percentage of cardiac output (CQt) to each organ was calculated as the amount of each

nuclides radioactivity in that organ divided by the total body count for that nuclide Blood flow to each organ was calculated as percentage of cardiac output times the cardiac output from the dye-dilution determination Peripheral and organ resistances were calculated by dividing the difference between mean arterial and mean venous pressure by flow

The raw data were tabulated and processed to yield the means and standard errors of means for each parameter Statistical significance was confirmed or denied where appropriate with the Student's t test for paired or unpaired data Changes were considered significant when the value for P was less than 0.05

Results

All animals were anesthetized and cooled uneventfully with changes in hemodynamic and blood gas parameters similar to those in the previously reported series were blood flow and distribution were studied during the cooling phase

Hemodynamic parameters during rewarming Hemodynamic blood gas and hematocrit data are shown in Table I Heart rate which was about 30% of unanesthetized control values in both groups at 20°C was significantly less than control until the completion of rewarming in the non arrested animals. Mean arterial pressure

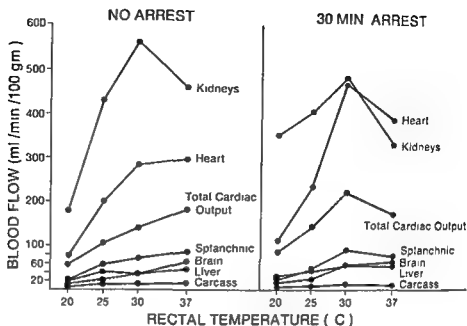


Fig 2 Absolute organ blood flows and total cardiac output during rewarming

resistance remained near 50% of control thereafter. Arrested animals showed an increase to control value at 25°, 30° and 37° C. Arrested animals had significantly greater carcass vascular resistance from non arrested animals at 25° and 37° C.

Distribution of cardiac output (Table II) In non arrested animals the %Qt distributed to the coronary circulation was decreased but insignificantly so, throughout rewarming. Coronary %Qt was significantly decreased in the arrested group at 20° C but thereafter increased to levels significantly greater than in non arrested animals at the completion of rewarming (37° C).

The percentage of cardiac output distributed to the brain was significantly reduced (60% of control) at 20° C in animals not subjected to circulatory arrest. Cerebral %Qt began to increase by 30° C and had returned to control at the completion of rewarming. Animals subjected to arrest had a significantly greater %Qt distributed to the brain than non arrested animals at 20° and 25° C. Furthermore, %Qt was not significantly different from control at any time during rewarming in arrested animals.

Renal %Qt was not significantly altered by rewarming in the non arrested group although absolute values tended to decrease between 30° and 37° C. In the arrested group the trend was to a decreasing renal %Qt which became significantly less than control value at the completion of rewarming.

Hepatic %Qt tended to be greater than control at 20° C with a decline to control by 37° C in non arrested animals. Arrested animals showed the opposite trend that is an initial decrease at 20° C with a steady increase thereafter. These trends although consistent were not statistically significant.

Splanchnic %Qt in non arrested animals increased during rewarming to significantly higher levels at 30° and 37° C. A similar trend was observed in the arrested group.

Carcass %Qt tended to decline in both groups during rewarming but the differences were not significant.

Changes in organ blood flow (Table II) Coronary flow which was significantly below control at 20° and 25° C increased with rewarming in the non arrested group. Arrested animals tended to have greater coronary flows than non arrested animals and at 30° C the difference was significant.

Cerebral blood flow was significantly below control until rewarming was completed in the non arrested group. Arrested animals showed significantly reduced flow at 20° and 25° C but at 30° C the trend was toward control values. At 37° C however flows had again decreased to levels significantly below control. When the two groups were compared cerebral flow was twice as great in arrested vs non arrested animals at 20° C and at 25° C.

Renal flows were subject to large individual

Table II Percentages of cardiac output (% Q) and absolute blood flows (mL/min/100 g tissue weight) to various organs and tissues*

| | | Unanesthetized control 37° C | Rewarming ether anesthesia | | | |
|---------------------|----|---------------------------------|-------------------------------|------------|------------|------------|
| | | | 20° C | 25 C | 30° C | 37° C |
| CO (mL/min) | NA | 1419 ± 144 | 370 ± 60 | 860 ± 112 | 1080 ± 143 | 1236 ± 103 |
| | A | 1633 ± 88 | 532 ± 66 | 907 ± 147 | 1322 ± 47 | 1041 ± 76 |
| Heart (% Q) | NA | 85 ± 16 | 48 ± 10 | 5.9 ± 1.2 | 6.9 ± 1.8 | 5.7 ± 0.2 |
| | A | 7.8 ± 0.5 | 5.6 ± 0.4 | 7.3 ± 1.2 | 9.2 ± 0.7 | 9.6 ± 1.1 |
| mL/min/100g | NA | 492 ± 101 | 77 ± 23 | 201 ± 26 | 284 ± 42 | 297 ± 27 |
| | A | 494 ± 70 | 113 ± 14 | 230 ± 81 | 469 ± 51† | 388 ± 58 |
| Brain (% Q) | NA | 4.4 ± 0.4 | 2.8 ± 0.2 | 2.5 ± 0.4 | 2.9 ± 0.3 | 4.4 ± 0.3 |
| | A | 4.3 ± 0.3 | 4.3 ± 0.8† | 4.6 ± 0.6† | 3.8 ± 0.8 | 4.8 ± 0.5 |
| mL/min/100g | NA | 71 ± 10 | 12 ± 5 | 23 ± 3 | 35 ± 3 | 63 ± 8 |
| | A | 77 ± 5 | 26 ± 5 | 44 ± 5 | 56 ± 13 | 54 ± 4 |
| Kidneys (% Q) | NA | 18.5 ± 3.0 | 15.1 ± 1.5 | 14.2 ± 2.0 | 16.2 ± 2.2 | 11.3 ± 1.1 |
| | A | 13.6 ± 0.8 | 18.5 ± 2.9 | 14.0 ± 1.6 | 10.5 ± 1.9 | 8.8 ± 0.9 |
| mL/min/100 g | NA | 833 ± 155 | 177 ± 25 | 431 ± 134 | 562 ± 102 | 459 ± 70 |
| | A | 809 ± 8° | 35° ± 60 † | 406 ± 41 | 482 ± 39 | 331 ± 25 |
| Liver (% Q) | NA | 6.3 ± 1.4 | 8.5 ± 1.3 | 7.0 ± 0.6 | 5.2 ± 1.1 | 6.8 ± 2.0 |
| | A | 7.4 ± 1.1 | 4.8 ± 1.0 | 4.8 ± 1.7 | 6.3 ± 2.8 | 8.7 ± 2.4 |
| mL/min/100 g. | NA | 58 ± 17 | 70 ± 5 | 39 ± 7 | 36 ± 8 | 50 ± 12 |
| | A | 83 ± 18 | 17 ± 4 | 24 ± 9 | 57 ± 19 | 62 ± 16 |
| Splanchnic (% Q) | NA | 23.1 ± 1.4 | 26.8 ± 4.2 | 29.9 ± 3.4 | 30.6 ± 3.0 | 31.7 ± 2.1 |
| | A | 23.2 ± 1.9 | 19.9 ± 2.6 | 25.1 ± 4.1 | 29.8 ± 5.2 | 31.8 ± 3.4 |
| mL/min/100 g | NA | 71 ± 16 | 21 ± 3 | 56 ± 9 | 71 ± 11 | 87 ± 14 |
| | A | 89 ± 16 | 24 ± 4 | 47 ± 13 | 91 ± 17 | 77 ± 11 |
| Carcass (% Q) | NA | 45.5 ± 2.8 | 50.1 ± 2.1 | 47.1 ± 3.7 | 43.1 ± 3.5 | 46.1 ± 1.3 |
| | A | 49.9 ± 2.6 | 51.0 ± 4.8 | 48.0 ± 2.5 | 45.5 ± 5.4 | 43.6 ± 4.1 |
| mL/min/100 g | NA | 19 ± 4 | 6 ± 2 | 12 ± 3 | 13 ± 3 | 16 ± 2 |
| | A | 17 ± 4 | 5 ± 1 | 8 ± 1 | 13 ± 3 | 10 ± 3 |

*The symbols for statistical analyses are described in Table I

Coronary vascular resistance in the non arrested group was at about 150% of control at 20° C during rewarming decreased rapidly to slightly below control at 25° C and decreased only slightly thereafter. These changes were not statistically significant due to large individual variation. In the arrested group coronary resistance was similar to control value at 20° C but was significantly reduced at 30° and 37° C.

Renal vascular resistance was not significantly changed from preanesthetic control throughout rewarming in the non arrested group. Arrested

animals had significantly decreased renal vascular resistance at 20° C but resistance increased during rewarming to levels significantly greater than in non arrested counterparts of the completion of rewarming.

Splanchnic vascular resistance was the most variable of the organ systems evaluated. In both groups hepatic resistance was below control throughout rewarming.

Carcass vascular resistance in the non arrested group was reduced at 20° C during rewarming. The reduction was significant at 25° C and

ry reduction in flow to other organs and a previous study in dogs showed no change in blood volume at the onset of rewarming.⁷ Thus it seems unlikely that the effects of surface rewarming on TVR and carcass vascular resistance at 20° C can be accounted for by major changes involving vasomotion.

The TVR in non arrested animals was similar at 25°, 30°, and 37° C during rewarming and was significantly less than the unanesthetized normothermic control value. While the influence of surface heating described above may explain generally lower resistances during rewarming than at comparable temperatures during cooling it also suggests that TVR should change progressively with rewarming instead of remaining stable at and after 25° C. We have examined other factors that are capable of influencing TVR during rewarming. These include (1) oxygen consumption which has been shown to be higher at comparable temperatures during rewarming;¹² (2) anesthetic level, which, as judged by clinical signs is the sum of the effects of anesthetic concentration and cold depression (circulatory arrest may also exert a depressive effect since arrested animals usually require less anesthetic during rewarming); (3) cardiac output which progressively rises during rewarming but was greater at 20° C and less at 37° C in arrested vs non arrested animals; (4) blood volume which is unchanged following rewarming in non arrested dogs but decreased in animals subjected to arrest;¹³ (5) plasma catecholamines, which are markedly elevated for a brief period following circulatory arrest at 20° C but are unchanged in non arrested dogs.¹⁴ While the interaction of these factors is not entirely understood it is clear that TVR differences during rewarming vs cooling and between the arrested and non arrested groups in this study involve varying degrees of functional autoregulation at deep hypothermic levels.

Blood flow in individual organs. Assessing the adequacy of blood flow to the brain is difficult since it shows little correlation with functional and histopathological changes.^{15, 16} In addition the level of cerebral blood flow necessary to maintain basal conditions may be considerably below the level necessary to provide maximal tissue reserves and hence the maximum possible safe circulatory occlusion time at a given temperature. Recent studies by Ohmura and associates¹⁷

and by Hagerdal and colleagues¹⁸ give credence to the concept that the integrity of the brain can probably only be accurately monitored on the metabolic or biochemical level. Until better monitoring methods are established however an interim approach involves comparing cooling and rewarming cerebral flows in arrested and non arrested animals. Using our technique of deep hypothermia¹² we have maintained surface cooled dogs at temperatures below 20° C for up to two hours following surface rewarming with no change—including such judgmental factors such as appetite, degree of activity, etc.—could be detected. Half term puppies cooled *in utero* and not arrested in mothers who were arrested for one hour have come to normal delivery,¹⁹ grown to adulthood and been cooled again and arrested for one hour and have not suffered detectable changes (unpublished data). These observations and other studies of cerebral oxygen consumption and metabolism²⁰ leave little doubt that cerebral blood flow during cooling is adequate with the method described herein.

During rewarming absolute cerebral blood flow was always greater than at equivalent cooling temperatures. Furthermore the cerebral %Q, absolute flow and cerebral vascular resistance data confirm a reactive hyperemia following resuscitation and rewarming in arrested animals that did not occur in non arrested animals.

In both groups of animals during rewarming coronary blood flow was consistently maintained at higher values than at comparable temperatures during cooling. These flows occurred despite differences in cardiac output and coronary vascular resistance strongly suggesting intact autoregulative function. Under normothermic basal conditions coronary venous oxygen content is very low so that an increased oxygen demand must be supplied by an increase of coronary blood flow. Similarly coronary blood flow must increase to compensate for decreased oxygen supply due to reduced oxygen content or other causes such as a shift in the oxyhemoglobin dissociation curve. During hypothermia the interaction of these factors may be complex; however the fact that myocardial oxygen requirement is determined by the amount and kind of cardiac work has yet to be disproven under conditions of hypothermia. At normothermia cardiac indices have been developed which relate cardiac work to oxygen consumption and hence to coronary flow. Such rela-

variations in both groups. It was apparent how ever that renal flow in both groups increased during rewarming from 20° to 30° C and then decreased with further warming to 37° C. Furthermore, arrested animals had significantly greater flows at 20° C than did non arrested animals.

Hepatic arterial flow in the non arrested group was approximately 30% of control at 20° C and increased with temperature to near control by 37° C. These changes were not statistically significant due to individual variations during the pre anesthetic control determinations. Arrested animals had significantly reduced hepatic flows at 20° and at 25° C with an increase toward control by 37° C.

Splanchnic blood flow increased throughout rewarming in both groups and was significantly greater than control in non arrested animals at 30° and at 37° C.

Carcass flows in both groups were significantly reduced from control values at 20° C. At 37° C carcass flow in arrested animals was still significantly reduced whereas it had returned to control in non arrested animals.

Discussion

Our previous report² discussed the effects of surface cooling and ether anesthesia on regional blood flow. It was also noted that only about five separate microsphere injections are practical on this basis. We elected to study the cooling and rewarming phases of deep surface hypothermia separately. While this approach comprises statistical comparisons between the cooling and rewarming phases, it has the advantage of doubling the number of observations over the whole procedure.

The present study reveals that rewarming is a complex process with vascular resistance output fraction to various organs and organ blood flow varying in response to both rewarming and circulatory arrest. At 20° C shortly after the initiation of surface rewarming the TVR in both arrested and non arrested animals decreased abruptly to approximately 50% of the levels seen at 20° C during cooling. As rewarming continued the TVR of non arrested animals stabilized at levels significantly below the awake control whereas arrested animals showed fluctuating generally higher TVR (Table I). Since cardiac output is only slightly (and insignificantly) greater in the arrested group at 20° C it seems

likely that rewarming *per se* exerts the dominant influence during the first few minutes of surface rewarming. In dogs cooled by ice-water immersion subcutaneous temperatures quickly fall to 10° C or less and skeletal (thigh) muscle also cools rapidly, the latter usually reaching 15° C while the core (brain, liver, rectal) temperature is at 20° C (unpublished data). During rewarming in a 40° C bath skin and skeletal muscle temperatures are normothermic or nearly so by the time core temperature has reached 25° C. The fact that whole body vascular resistance and carcass vascular resistance change in a parallel fashion at the initiation of rewarming again strongly suggests the dominant role of surface heating as a cause of the abrupt reduction of TVR.

There is considerable evidence that the above changes with the induction of surface rewarming are not entirely the direct vasodilative effect of heat. Several studies have shown that both cooling³ and ether anesthesia⁴ can result in maximal peripheral capillary and arteriolar dilatation in which case significant cutaneous or skeletal muscular vascular dilatation should not occur with the induction of surface rewarming. Furthermore, the relationships between temperature and blood viscosity have been well documented⁵ and it has been observed that blood viscosity rises rapidly with a decrease in temperature below 27° C.⁶ As surface cooling is started, skin temperature decreases rapidly to near 0° C while the core is still normothermic, creating a temperature and temperature-induced viscosity gradient in the central vs the peripheral vascular compartment. Surface rewarming quickly reverses this gradient, thus the immediate decrease in skin and skeletal muscle vascular resistance noted in this study at the onset of surface rewarming may be the result of reducing blood viscosity in the vessels closest to the surface. This effect would potentially improve venous return to the heart and tend to explain (1) why cardiac output is greater at 20° C during rewarming than at 20° C during cooling and (2) why cardiac output begins to increase during surface rewarming before a detectable increase in core temperature is evident.

Carcass vascular resistance is halved by the initiation of surface rewarming at 20° C. If this is the result of vascular dilatation then intravascular volume would increase accordingly or be compensated for by a decrease in the volume (vasoconstriction) in other organ systems. The current study shows that there is no compensatory

ng rewarming especially in arrested animals CO appeared to be similar to those noted at comparable cooling temperatures until 30° C during rewarming thereafter CO did not fully recover to awake control levels. These data suggest that regional flow is redistributed from the carcass and renal circulations to cerebral and coronary circulations in response to hemodynamic alterations during surface rewarming. It was concluded that autoregulative responses to both circulatory arrest and hemodynamic factors are elicited during surface rewarming from deep hypothermia to 10° C with the method described.

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relationships have not been well established during hypothermia so that changes in coronary flow with various cooling methods have resulted in much conjecture. Studies by others have shown that coronary flow and coronary resistance may increase or decrease depending upon temperature and the method of cooling.^{2, 26} We suggest however that there is no reason to believe that the principles of normothermic coronary autoregulation (primarily oxygen demand) do not function within the temperature range than can be achieved with surface cooling (18° to 20° C). It also seems likely that a better understanding of the determinants of myocardial oxygen demand during hypothermia would resolve many of the apparent discrepancies regarding coronary flow reported in the literature.

The present study revealed coronary vascular resistance and flow patterns consistent with a hyperemic response following circulatory arrest that was not evident in non-arrested animals. In previous studies using dogs under similar conditions we found that plasma catecholamines are elevated immediately following circulatory arrest²⁷ and that coronary A-V lactate balance became negative. These data support the conclusion that the coronary circulation does respond to metabolic stimuli even at 20° C.

Our data suggested that renal blood flow during cooling paralleled the decline in cardiac output since the renal $\dot{V}Q_t$ was unchanged. During rewarming the significantly greater absolute renal flow in arrested animals at 20° C as compared to immediately rewarmed animals probably represents a hyperemia. As rewarming progressed the renal $\dot{V}Q_t$ decreased especially in arrested animals so that absolute flow was below control values at 37° C. The cause of these reduced flows is explained by the slightly reduced cardiac output²⁸ and blood and plasma volumes that are known to occur following rewarming with this hypothermia method. The absence of primary post-rewarming renal failure and histopathologic changes in dogs subjected to a similar protocol is consistent with the hypothesis that the transient shift of flow away from the kidneys is related to cardiovascular dynamics and blood volume rather than to low temperature *per se*. In fact Tempel and associates²⁹ have shown that changes in these parameters are sufficient to explain decreased renal function at low temperatures during both induced hypothermia and normal hibernation.

From a practical clinical standpoint such considerations imply that the cardiovascular and/or blood volume status rather than primary kidney alterations should be suspected as the cause of renal malfunction in the post-hypothermic patient with poor urine output. Additional studies should be done to confirm and expand these relationships and their validity in the patient with congenital cardiac disease following repair under deep hypothermia.

Interpretation of liver and splanchnic flow data was hampered by large individual variations. While in part related to methodology, the greater variance in these systems might be expected because they play a major role in terms of immediate circulating volume adjustments. Morphologic studies in dogs revealed some dilatation of hepatic sinusoids after cooling to 18° C³⁰ and we have recently shown that the hepatic sinusoids are the site of the platelet sequestration phenomenon associated with surface cooling.³¹

This study demonstrates that the regional distribution of blood flow is not necessarily similar at specific temperatures depending (1) upon the stage of the procedure (cooling as opposed to rewarming) and (2) upon the addition of a period of circulatory arrest prior to rewarming. This knowledge and the microspheres technology if expanded will likely provide a basis for comparing hypothermia techniques especially if low temperature regional flow requirements can be ascertained and correlated to functional and histopathologic changes following rewarming.

Summary

Regional blood flow and distribution of cardiac output (CO) were evaluated by the radioactive microsphere technique in rhesus monkeys during surface rewarming following the induction of deep hypothermia (20° C) under deep ether anesthesia. A comparison of animals subjected to 30 minutes of circulatory arrest and those not arrested revealed cerebral, coronary and renal vascular resistance and flow patterns consistent with a hyperemic response to circulatory arrest at 20° C. Throughout rewarming cerebral and coronary absolute flows tended to be at or above the flows noted at comparable cooling temperatures in a previous study. Renal flow fraction ($\dot{V}Q_t$) were well preserved during rewarming to 30° C but a decrease was observed thereafter. Carcass (muscle-skin-bone) $\dot{V}Q_t$ was also reduced follow-

Table I Serum and CSF quinidine concentrations in eight human subjects

| Subject | Age/sex | Serum quinidine total (µg/ml) | Percent unbound | Serum quinidine unbound (µg/ml) | CSF quinidine (µg/ml) | Ratio of CSF to unbound serum concentrations |
|-------------|---------|-------------------------------|-----------------|---------------------------------|-----------------------|--|
| 1 | 31/M | 2.27 | 13.1% | 0.30 | 0.013 | 0.04 |
| 2 | 24/M | 1.25 | 18.1% | 0.23 | 0.039 | 0.17 |
| 3 | 41/M | 2.96 | 21.3% | 0.64 | 0.071 | 0.11 |
| 4 | 70/M | 1.98 | 22.2% | 0.44 | 0.079 | 0.18 |
| 5 | 29/F | 0.91 | 13.2% | 0.12 | 0.011 | 0.09 |
| 6 | 49/M | 2.14 | 17.4% | 0.37 | 0.053 | 0.14 |
| 7 | 38/F | 0.74 | 18.2% | 0.13 | 0.048 | 0.37 |
| 8 | 23/M | 1.78 | 16.7% | 0.30 | 0.054 | 0.18 |
| Mean (± SE) | | 1.75 (± 0.26) | 17.5% (± 1.2%) | 0.32 (± 0.06) | 0.048 (± 0.009) | 0.16 (± 0.03) |

Table II Relation of unbound serum quinidine to total serum and CSF concentrations in four dogs

| | Animal number | | | |
|--|----------------------|--------------------|----------------------|---------------------|
| | 1 | 6 | 7 | 8 |
| Mean percent unbound quinidine (range) | 18.8% (15.0-25.5) | 7.9% (5.5-12.5) | 14.8% (11.0-24.6) | 15.6% (9.4-26.6) |
| Correlation coefficient for unbound vs total serum quinidine | 0.67 | 0.44 | 0.16 | 0.63 |
| Mean ratio of CSF to unbound serum quinidine | 0.45 | 0.37 | 0.46 | 0.46 |
| Correlation coefficient for CSF vs unbound serum quinidine | 0.89* | 0.81 | 0.87 | 0.64 |

* $p < 0.1$ $p < 0.05$

of quinidine base was injected intravenously over a period of one minute. Samples of blood (4 to 5 ml) and CSF (1 to 3 ml) were simultaneously taken before the infusion and at the following post infusion times: 5, 10, 15, 30 and 45 minutes, 1, 1.5, 2, 2.5, 3, 3.5 and 4 hours, then hourly for up to 8 hours after the dose. Serum and CSF were stored at -20°C until the time of assay.

After an interval of two weeks, serum quinidine kinetics were studied again without anesthesia in two of the four dogs to assess the effect of the anesthetic procedure. CSF was not sampled.

In vitro study The partitioning of quinidine between water and *n*-octanol at physiologic pH was determined in vitro. A solution of quinidine sulfate (5 µg/ml) in phosphate buffer (pH 7.4) was shaken with an equal volume of octanol. The quinidine concentration in the aqueous phase was determined before and after the octanol extraction.

Analysis of samples Quinidine concentrations in all samples (serum, CSF or phosphate buffer)

were determined by modification of the double extraction spectrophotofluorometric technique. The extent of quinidine protein binding in each serum sample was determined by equilibrium dialysis.⁹

Results

Percent unbound quinidine in serum among the eight human subjects ranged from 13.1 to 22.2% (Table I). CSF concentrations were always lower than unbound serum levels at the time of sampling. The mean (± SE) CSF to unbound serum concentration ratio was 0.16 (± 0.03) with a range of 0.04 to 0.37.

The mean percent unbound serum quinidine among the four dogs ranged from 7.9 to 18.8% (Table II). However, percent unbound serum quinidine increased with increasing total quinidine concentrations (Table II, Fig 1), consistent with concentration dependent protein binding. Quinidine appeared promptly in CSF of all four dogs (Fig 2). Quinidine concentrations in serum

Entry of quinidine into cerebrospinal fluid

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Central nervous system (CNS) toxicity is commonly associated with the use of quinidine derivatives in clinical practice.¹⁻⁴ The characteristic syndrome of mild cinchonism includes headache, tinnitus and blurring of vision. More severe cinchonism can include marked auditory and visual disturbances as well as behavioral and neurologic disorders.^{5,6} Gastrointestinal toxicity attributable to quinidine (diarrhea, nausea, vomiting) may also reflect effects on the CNS inasmuch as these symptoms can be caused by parenteral administration of quinidine.⁷ Furthermore, quinidine can produce emetic movements in ether-anesthetized animals.⁸

Despite the clinical importance of quinidine's

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central toxicity, few data are available on the rate and extent of its entry into the CNS. The present study assessed simultaneous serum and cerebrospinal fluid concentrations of quinidine in a series of human subjects. We also studied the rate and extent of quinidine entry into cerebrospinal fluid in dogs.

Methods

Human studies. Eight volunteers scheduled for diagnostic lumbar puncture participated after giving informed consent. Subjects received 500 mg of quinidine bisulfate at 12 hours and again at 2 hours prior to the procedure. A sample of venous blood together with a 1 to 2 ml aliquot of cerebrospinal fluid (CSF) were obtained simultaneously. Blood samples were allowed to clot at room temperature, then were centrifuged. Serum and CSF were stored at -20°C until the time of assay.

Animal studies. Four adult mongrel dogs (20 to 32 kilograms) were anesthetized with intravenous pentobarbital (30 mg/kg), intubated and ventilated with a Harvard respirator to maintain arterial oxygen tension within normal limits. Body temperature was maintained with a heating pad and fluid losses were approximately replaced with intravenous 0.9% sodium chloride solution. A 75 cm spinal needle (19 gauge) was inserted into the cisterna magna to allow repeated sampling of CSF.

Quinidine gluconate † equivalent to 10 mg/kg

Chundin Durules, Asta Chemicals, Wed 1/Holst in W Germany. Contains 99% quinidine base by weight.

†Eli Lilly and Co, Indianapolis, Indiana, USA.

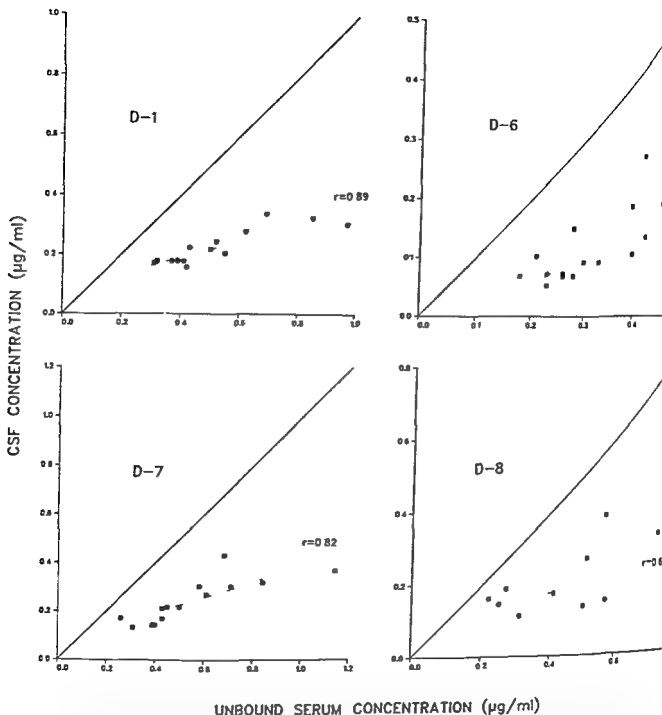


Fig 3 Simultaneous unbound serum and CSF concentrations of quinidine in four animals. Solid diagonal lines are the theoretical functions of identity (unbound serum = CSF concentration). Actual data points always fall below the line (unbound serum greater than CSF concentration). Dashed lines were determined by least-squares regression analysis.

CSF concentrations were considerably lower than unbound serum concentrations in each of the human subjects studied. The findings were confirmed when the rate and extent of quinidine entry into CSF was studied in dogs. The results of the animal studies are not likely to reflect non-equilibrium conditions due to slow entry of quin-

idine into CSF. In fact, quinidine appeared very rapidly in dog CSF following which CSF and unbound serum concentrations declined in parallel with a nearly constant ratio maintained between the two. This strongly suggests that distribution equilibrium was rapidly attained. In the human studies, the clinical contrain-

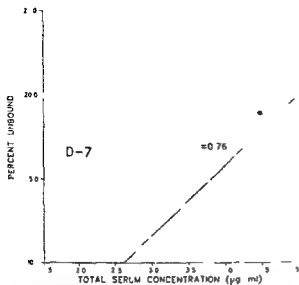


Fig 1 Relation of the extent of quinidine protein binding to total serum quinidine concentration in Dog No. 7. Note that binding decreases with increasing total serum concentration ($r = 0.6$ $p < 0.01$)

(unbound and total) and in CSF declined in parallel. CSF quinidine concentrations were always less than unbound serum levels (Figs 2 and 3) although the two were highly correlated in all four animals. The mean ratio of CSF to unbound serum quinidine ranged from 0.37 to 0.45 among the four dogs (Table II).

The elimination half life of quinidine in the two animals studied both without and with barbiturate anesthesia was prolonged by anesthesia from 3.7 to 16.2 hours and from 5.3 to 12.3 hours respectively (Fig 4). Total quinidine clearance was correspondingly reduced during anesthesia. The findings suggest that some aspect of the general anesthetic procedure is associated with marked impairment of quinidine clearance.

The ratio of quinidine concentrations measured in the aqueous phase before and after mixing with octanol was 1.33 indicating greater than 99% partitioning into octanol at physiologic pH.

Discussion

Physicochemical factors influencing the passage of drugs and plasma constituents from blood to CSF are known to include the degree of drug binding to plasma protein, the degree of ionization at physiologic pH, and the lipophilicity of the undissociated molecule. Many drugs are moderately lipophilic when undissociated and at physiologic pH are at least partly undissociated.

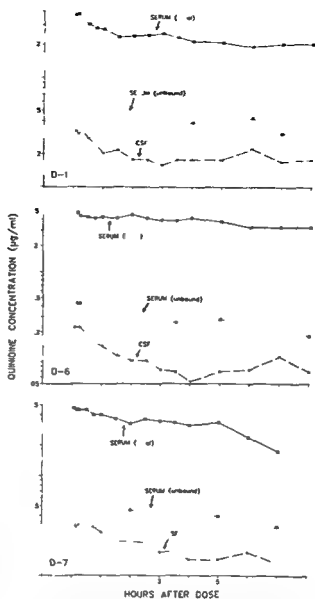


Fig 2 Concentrations of quinidine in serum (unbound and total) and in CSF following intravenous quinidine (10 mg/kg of quinidine base) administered at time zero to three representative dogs.

If the passage of such compounds into CSF occurs by passive diffusion, then CSF concentrations after attainment of distribution equilibrium are approximately equal to the unbound concentration in plasma.¹⁹ In the case of quinidine, a weak organic base, its octanol/water partition characteristics suggest that the fraction of total drug existing as the lipophilic free base at physiologic pH is sufficient to favor rapid equilibration of unbound serum quinidine with CSF if passive diffusion alone governed the process.¹⁷ However,

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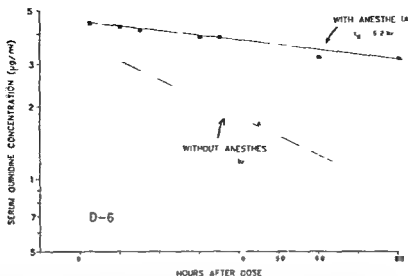


Fig 4 Total serum quinidine concentrations in Dog No 6 after intravenous injection of quinidine (10 mg/kg of quinidine base) on two occasions, with and without concurrent general anesthesia. The elimination half life ($t_{1/2}$) was more than four times longer when quinidine was given during general anesthesia.

requiring lumbar CSF sampling might lead to lower CSF quinidine concentrations than those present at sampling sites closer to the brain due to the time required for circulation of CSF.⁹ However, this is unlikely to account for the large differences between unbound serum and CSF quinidine concentrations. The findings therefore suggest that passage of quinidine into CSF is not determined simply by passive diffusion. It may be that quinidine participates in an active transport such as that known to remove from CSF other basic substances including morphine, codeine, atropine and gentamicin.²⁵

Total quinidine clearance in the dog studies was markedly lower in the anesthetized state when compared to values measured upon retesting in the unanesthetized condition. This could be explained either by a direct inhibitory effect of pentobarbital upon hepatic biotransformation of quinidine or by hemodynamic changes associated with the anesthetized condition. In any case, it is clear that kinetic properties of drugs established in studies of conscious animals or humans are not necessarily applicable during general anesthesia.

Summary

Some of the unwanted effects of quinidine commonly occurring in clinical practice involve the central nervous system. We therefore assessed the rate and extent of quinidine passage into

cerebrospinal fluid (CSF) in humans and dogs. In eight human subjects receiving oral quinidine therapy, lumbar CSF quinidine concentrations averaged 16% of unbound serum concentrations (range 4% to 37%). The findings were confirmed when simultaneous serum (total and unbound) and CSF quinidine concentrations were followed for up to 8 hours after a single intravenous dose of quinidine in anesthetized dogs. Quinidine appeared promptly in CSF of all animals, but CSF concentrations averaged only 37% to 46% of unbound serum levels. The *in vitro* octanol/water partition coefficient for quinidine at physiologic pH was greater than 100, indicating that unbound quinidine should readily traverse the blood-brain barrier. Thus, passage of quinidine into CSF appears not to be governed by passive diffusion alone. Quinidine may participate in an active transport system such as that which removes certain other basic substances from CSF.

We are grateful for the assistance of Ann Werner, Kate Franke, Lawrence J. Moschitto, and Dr. Dean S. MacLaughlin. Dr. MacLaughlin is supported by Grant GM 23430 to the Boston Collaborative Drug Surveillance Program. Drs. Reynold Spector, William Oldendorf, and Stanley Rapoport provided valuable critical comments.

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in a chronic alcoholic patient coincidental with a serum aprindine level of 3 $\mu\text{g/ml}$. In another study, those patients developing psychosis while on aprindine had previous histories of mental illness or hypoxic brain damage.² Other authors feel that the neurologic side effects of aprindine generally did not occur at serum levels less than 1 $\mu\text{g/ml}$ without fine tremor and dizziness occurring prior to intention tremor ataxia and the other CNS manifestations.³ Here, patients reporting hallucinations had serum levels of 1.6 to 3.6 $\mu\text{g/ml}$.

Our patient had no psychiatric history and on previous hospitalization both in the CCU and on the floors had never exhibited any signs of depression or bizarre behavior. The sudden onset of psychosis concurrent with aprindine administration and its subsequent complete resolution after discontinuing the drug is strong evidence of drug-induced psychosis. The serum level of 1.05 $\mu\text{g/ml}$ is only borderline therapeutic and does not approach the levels previously reported in patients with psychosis while on aprindine. In addition, she did not exhibit any other CNS side effects associated with aprindine toxicity. We conclude that psychosis may appear as an isolated side effect of aprindine administration at relatively low serum levels. The drug's efficacy in suppressing ventricular arrhythmias, especially in patients with the mitral valve prolapse syndrome, is reinforced. It remains however an agent with

significant side effects that restricts its use to patients in whom other antiarrhythmic therapy has been unsuccessful.

Summary

A young woman with mitral valve prolapse and ventricular tachycardia refractory to numerous antiarrhythmics received a trial of aprindine. During the course of treatment she developed a severe psychotic reaction that resolved after the drug was stopped. Her psychosis was unassociated with the other dose-related neurological side effects of aprindine and occurred at borderline therapeutic levels of the drug.

We wish to thank Dr. Thomas Rommer for referring this patient to us for the therapeutic trial.

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Aprindine psychosis

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Aprindine is an anti arrhythmic drug presently being used in clinical investigation for the treatment of refractory supraventricular and ventricular tachycardia. The various side effects reported including agranulocytosis, cholestatic hepatitis and neurological reactions such as tremor and ataxia are dose related and reversible. We report here a case of acute psychosis developing at borderline low therapeutic levels of aprindine.

Case report

The patient is a 29 year-old female who was in previous good health and who six months prior to this admission developed coughing and wheezing while at work. She was examined by a physician who discovered an irregular pulse and admitted her to the hospital for further work up. Initial ECG revealed frequent PVCs with coupling and the patient was admitted to the CCU for observation. Evaluation by echocardiogram at that time disclosed the presence of mitral valve prolapse. The electrocardiogram showed frequent IVCs and non specific ST T wave changes in Leads II, III and aV with normal QT interval. CBC, electrolytes, BUN, glucose, calcium, magnesium, cardiac enzymes, arterial blood gases and ventilation-perfusion lung scan were all normal. Holter monitoring revealed frequent PVCs, bigeminy, trigeminy, couplets and several runs of ventricular tachycardia lasting as long as 12 to 15 seconds. For control of palpitations and the arrhythmia, multiple combinations of Inderal (propranolol HCl), Norpace (disopyramide), dilantin and quinidine were used. The patient was discharged on Norpace 300 mg orally every 6 hours and Inderal 100 mg orally every 6 hours.

During the ensuing 5 months she was followed as an outpatient. Because of persistent ventricular tachycardia and complaints of palpitations she was readmitted to the Newark Beth Israel Medical Center for a trial of aprindine. She was taking dioxin 0.25 mg daily, propranolol HCl 40 mg every 6 hours and quinidine gluconate 1 tablet every 8 hours.

She had not been on any other medications except for oral contraceptives which were stopped 5 months prior to admission. She is the working mother of three children with no history of depression or psychosis. She neither smoked nor used alcohol.

Physical examination revealed a young female in no distress with an irregular pulse of 76/minute. Lungs were clear. Examination of the heart disclosed a non-ejection click, with a late systolic murmur on standing. The remainder of the examination was unremarkable.

All medication was stopped for 24 hours and the patient was placed in the CCU. After baseline CBC, electrolytes, bilirubin, SGOT, SCPT, alkaline phosphatase and T were obtained, aprindine was started orally. On day one 300 mg was given in three doses on day two 100 mg was given in two doses on day three 200 mg was given in two doses. From the fourth day she was maintained on aprindine 75 mg orally twice a day. A marked therapeutic response was noted with only single PVCs on her Holter monitor tracings.

On the sixth day of therapy she became extremely agitated, anxious and combative. She had delusions of having died in her sleep and thought she was being poisoned through the air conditioning. At this time her physical examination was unchanged. She had no tremor, ataxia or nystagmus.

She was seen in psychiatric consultation and was felt to be having an acute psychotic reaction possibly on a toxic basis. Her serum chemistries, CBC, liver and cardiac enzymes were all within normal limits. An aprindine level drawn at that time was 1.05 µg/ml (Eli Lilly Laboratories). The aprindine was withheld and over the next 3 days her mental status returned to normal.

Discussion

Previous reports of hallucinations and psychosis during aprindine therapy were in patients in whom either toxic serum levels were achieved with accompanying tremor, ataxia or nystagmus or in clinical situations where the etiology of the psychosis was impossible to ascertain.¹ Hage, Meyer and colleagues² in their clinical studies of aprindine in patients with acute myocardial infarctions found three patients with disorientation, hallucinations and nightmares. Aprindine levels were measured in two of these and were greater than 3 µg/ml. Delirium tremens appeared

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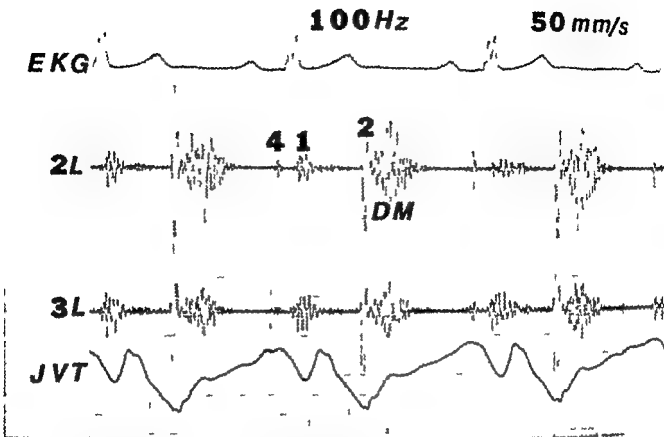


Fig 1 Phonocardiogram showing a fourth heart sound and a diastolic murmur following the pulmonic component of the second sound. JVT = jugular venous tracing

ventricle was dilated. Cardiac catheterization data appear in Table I. The pressure contour in the pulmonary artery was strikingly similar to that of the right ventricle, consistent with severe pulmonic regurgitation. Injection of contrast material in the pulmonary artery demonstrated 4 plus pulmonic regurgitation. Selective injection of both the right ventricle and pulmonary artery demonstrated a 2 by 3 cm accumulation of dye in the right ventricular outflow tract which was best seen in diastole (Fig 4). The contrast material appeared to be trapped within a structure or mass. A small but prominent calcification was noted adjacent to this accumulation of contrast material. A tumor was judged to be present together with severe pulmonary regurgitation and surgical intervention was recommended.

Significant dilatation of the pulmonary artery and right ventricular outflow tract was noted at surgery. Following right ventricularotomy a tumor was found. There was a small 5 mm in diameter calcified polyp-like mass on the septal side of the right ventricular outflow tract (Fig 5A). Pulmonary arteriotomy revealed a tricuspid pulmonic valve with the left leaflet intact. The remaining leaflets had large fenestrations occupying approximately 60% of their area (Fig 5B). The valve tissue was thin and glistening. The margins of the leaflets were smooth with normal endothelialization and no evidence of previous infection. Primary closure was accomplished. The postoperative course was unremarkable. All blood cultures before and at the time of surgery were negative.

Postoperatively the patient had a grade I/VI systolic ejection murmur and a grade II/VI harsh diastolic murmur along the left sternal border. Neither M mode echocardiogram (Fig 2B) nor 2 D echo revealed any mass or abnormal reflectance in the right ventricular outflow tract. Repeat cardiac catheterization (Table I) revealed normal pulmonary arterial pressure contours and 2 plus pulmonic regurgitation. No abnormal accumulation of contrast material occurred in the right ventricular outflow tract.

The patient is currently nine months postoperative and functions at full activity but continues to have physical findings of mild pulmonic regurgitation.

Discussion

M mode and more recently two dimensional echocardiography have assumed paramount importance in the evaluation of intracardiac tumors. The accuracy of these techniques to diagnose primary cardiac tumors as well as extracardiac masses is impressive. Occasional reports exist in which other structures including mitral stenosis, nonthrombotic masses on the mitral valve, mitral valve prolapse, and ventricular pacemaker wires can mimic intracardiac tumors.

'Pseudo tumor' of the right ventricular outflow tract and congenital pulmonary valve regurgitation A case report*

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In recent years M mode and two dimensional echocardiography have greatly enhanced our ability to recognize intracardiac tumors noninvasively. However the limitations as well as the usefulness of this technology warrant emphasis.

Case report

This asymptomatic 26-year-old man was referred for evaluation of a heart murmur. There was no history suggestive of infective endocarditis, scarlet fever, rheumatic fever, or drug abuse. Cardiac murmurs which were thought to be systolic were heard at 19 and 18 years of age.

Physical examination revealed a blood pressure of 120/80/75 mm Hg. The neck veins were flat at 45 degrees incline with a dominant "a" wave. Carotid and peripheral pulses were full and equal and there was no evidence of cyanosis, clubbing, or edema. The chest was clear. The point of maximum impulse was in the fifth left intercostal space at the mid clavicular line. The first heart sound was of normal loudness as was the second heart sound which demonstrated physiologic splitting. No ejection clicks were present. A fourth heart sound was best heard along the lower left sternal border. There was a short high frequency mid systolic murmur and a harsh middle frequency grade III/VI diastolic murmur along the left sternal border (Fig 1). Both murmurs increased with inspiration.

The chest x ray was normal. The electrocardiogram demon-

strated a vertical axis and was within normal limits. The M mode echocardiogram demonstrated dense echoes posterior to the pulmonic valve during diastole consistent with a right ventricular outflow tumor (Fig 2A). Other sections of the M mode echocardiogram failed to demonstrate right ventricular enlargement, paradoxical septal motion, or fluttering of the anterior leaflet of the tricuspid valve. Wide angle two-dimensional (2D) echocardiography (Fig 3) revealed a prominent reflectance in the right ventricular outflow tract which measured approximately 2 by 3 cm in diameter and imaged only during diastole. The motion of the structure was that of the surrounding right ventricular outflow tract. The bright reflectance or "mass-like" structure was always below the pulmonary valve and demonstrated no apparent involvement of either the valve or pulmonary artery. The real time 2D echocardiograms of the pulmonary valve were normal. In contrast to the appearance of the M mode echocardiogram, the right

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Table 1 Pre operative (column A) and postoperative (column B) cardiac catheterization findings

| | A | | B |
|------------------------|--------------------------|------------|----------------------------|
| | Pressure (mm Hg) | Saturation | Pressure (mm Hg) |
| Superior vena cava | | 70% | |
| Right atrium | a = 11 v = 9 m = 9 | 73% | a = 14 v = 14 m = 12 |
| Right ventricle | 37/11 | | 38/12 |
| Pulmonary artery | 32/12 m = 19 | 74% | 36/16 m = 20 |
| Pulmonary artery wedge | m = 10 | | |
| Left ventricle | 129/13 | | |
| Aorta | 129/72 m = 96 | 96% | |

Hydrogen inhalation circulation time in the pulmonary artery was normal.

strated a vertical axis and was within normal limits. The M mode echocardiogram demonstrated dense echoes posterior to the pulmonic valve during diastole consistent with a right ventricular outflow tumor (Fig 2A). Other sections of the M mode echocardiogram failed to demonstrate right ventricular enlargement, paradoxical septal motion, or fluttering of the anterior leaflet of the tricuspid valve. Wide angle two-dimensional (2D) echocardiography (Fig 3) revealed a prominent reflectance in the right ventricular outflow tract which measured approximately 2 by 3 cm in diameter and imaged only during diastole. The motion of the structure was that of the surrounding right ventricular outflow tract. The bright reflectance or "mass-like" structure was always below the pulmonary valve and demonstrated no apparent involvement of either the valve or pulmonary artery. The real time 2D echocardiograms of the pulmonary valve were normal. In contrast to the appearance of the M mode echocardiogram, the right

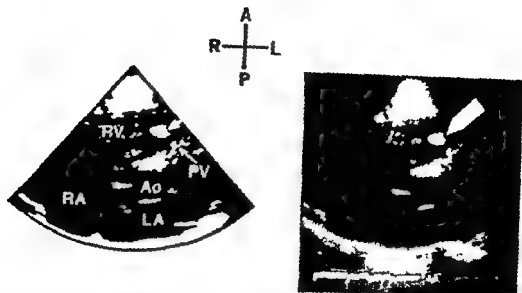


Fig 3 Two-dimensional echocardiogram of right ventricular (RV) outflow tract revealing dense echoes in RV outflow tract beneath the pulmonic valve (arrow). RA = right atrium Ao = aorta LA = left atrium PV = pulmonic valve A = anterior P = posterior R = right L = left

In retrospect the dense reflectances observed on both M mode and 2 D echo studies in the right ventricular outflow tract during diastole were generated by the 5 mm calcified polyp like mass. This small lump which contained no tumor cells was thought to be consistent with a jet lesion secondary to the long standing congenital pulmonary insufficiency. Because of its small size and the normal motion of the contracting right ventricle the calcium moved out of the path of the echo beam during systole.

Because of beam width resolution error the mass like reflectance on M mode echo appeared to be involving or much closer to the pulmonic valve compared to what was actually found. Motion and thickness of pulmonic valve leaflets were confirmed to be normal with 2 D echo and the structure in question did not involve or attach to the valve. In retrospect the obvious site of calcification on fluoroscopy should have alerted the echocardiographer that the apparent mass on 2 D imaging may have been generated by the calcium.

The echocardiographic interpretation error was compounded by the localized accumulation of contrast material on the angiogram in the same region of the right ventricular outflow tract. This localized trapped dye was thought to be related to the polypoid mass whereas in retrospect it was actually an unusual accumulation of dye amid trabeculations of the dilated



Fig 4 Angiography of the right ventricular outflow tract seen from a lateral view demonstrating an oval accumulation of contrast material (arrow) beneath the pulmonic valve

outflow tract fortuitously directed by the two large fenestrations in the pulmonic leaflets. There was no relationship between the small calcified lesion and the nearby accumulation of contrast material.

In the absence of any other abnormality involving the pulmonic valve it is not surprising that both M mode and 2 D echo studies revealed the valve to appear normal. Echocardiography is quite insensitive to identify isolated pulmonary valve insufficiency.

Isolated congenital pulmonic valvular regurgitation is a rare anomaly, more frequently congenital

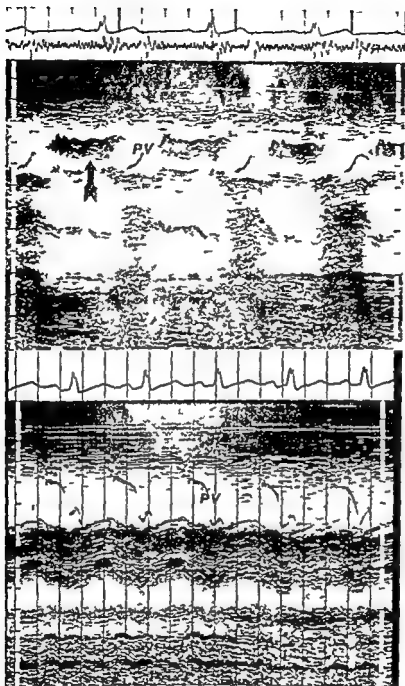


Fig 2 A (top panel) M mode echocardiogram of pulmonic valve shown, dense echoes beneath the pulmonic valve (PV) during diastole (arrow) B (bottom panel) M mode echocardiogram of pulmonic valve (PV) postoperatively demonstrating absence of dense reflectances beneath pulmonic valve seen preoperatively The A wave amplitude is prominent

The technical problems created by side lobe artifacts of 2 D echo images and beam width resolution errors of M mode studies are well recognized. It is also well known that prosthetic materials, wires, catheters, and calcium will

generate very prominent reflectances when the beam intersects them. Accordingly, the gain settings of the equipment must be reduced to prevent the respective structure or calcium from appearing much larger than actual size.

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Fig 5 A Small calcified mass (arrow) found at surgery on the septal side of the right ventricular outflow tract B Pulmonary valve at time of surgery demonstrating large fenestrations in pulmonary valve leaflets with normal surrounding valve tissue

ital pulmonic regurgitation is associated with a ventricular septal defect with or without pulmonic stenosis.¹¹ The large fenestrations causing pulmonic regurgitation in our case have not been reported previously. Fenestrations are usually seen as oval defects 0.1 to 0.3 mm in diameter and are of no hemodynamic importance.¹ Common causes of congenital pulmonic regurgitation include bicuspid valve,¹² supernumerary valves¹³ and agenesis of the valve.¹⁴ The findings at surgery excluded infective endocarditis as the cause of pulmonic regurgitation in our patient. Isolated congenital pulmonic regurgitation of a mild degree as presently found in our patient is associated with a very favorable prognosis.

Summary

The M mode and 2 D echocardiographic features of an unusual case of a pseudo tumor of the right ventricular outflow tract are reported. The unique pathologic findings of the pulmonary valve with congenital fenestrations and the clinical implications of this pseudo tumor are discussed. Whenever calcification is

noted at fluoroscopy to exist in a region or structure being evaluated by echocardiography, caution must be taken to avoid overestimating the size. Indistinct dense reflectances without specific motion or appearance of a mass further helps to distinguish the reflectances from an actual structure of significance. Furthermore, all clinical, angiographic and echocardiographic information must be interpreted together when either the angiogram or the echocardiogram is confusing and potentially misleading.

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their action as being anti infarct by an analogy with the term anti arrhythmic

Definitions Myocardial Infarction and Infarct Size

Infarct size is difficult to define because both infarct and size are not necessarily clear entities. The history of the use of the term myocardial infarct has been traced by Wartman¹⁰; it was first used in 1689 to indicate a vessel stuffed in — i.e. occluded. Later the association of regional tissue necrosis and vascular occlusion came to be called infarction i.e. massive regional necrosis caused by obstructive arteriosclerosis.¹⁰ Histologically there was a coagulation necrosis. But room was also left for the occurrence of noncoronary necrosis.¹⁰

Subsequently the tight association between an occlusive lesion and regional necrosis has become controversial. Thus some evidence shows that (1) histologic features of coagulation necrosis can occur without associated acute occlusion especially but not exclusively in smaller infarcts or subendocardial lesions^{11, 12} and that (2) in addition to coagulation necrosis other types of necrosis can be recognized in particular contraction band formation or myocytolysis¹³ which occurs around the border of human infarcts¹ and may be due to catecholamine induced hypercontraction of the cell.¹⁴ Other authors hold that the causative thrombus can regularly be found if searched for with sufficient care and vigor.^{15, 16} Thus the relation between the thrombus and the histological lesion is by no means settled.¹⁷ One recent authoritative view is that the thrombus although found in just over half (60%) of the patients dying with acute transmural infarction is usually absent in patients dying soon after the onset of symptoms.¹⁸ Thus (1) myocardial infarction need not necessarily be associated with a vascular occlusion lesion nor need the histological damage be limited to the classical coagulation necrosis and (2) the term infarct therefore touches on certain very controversial vascular and histologic definitions.

Nor is the use of the term infarct size any less free from problems of definition. In the strict sense the volume of infarcted tissue should be expressed as a percentage of the total but experimental studies have generally used indirect indices such as the number of sites with electrocardiographic evidence of ischemia (ST eleva-

tion) or the degree of enzyme (creatinine kinase) depletion, and only seldom has true pathological size been quantified. Pathological quantification is made more difficult by the heterogeneity of the lesion with an admixture of living and dead cells.¹⁰ Quantification is more easily using the degree of myocardial depletion of creatine kinase which has however, been linked only to the severity of coagulation necrosis¹ while the relation if any, to myocytolysis (hypercontracted dead cells) remains to be determined. It should also be noted that the size of the infarct assessed 24 hours post ligation is not necessarily the same as that of the eventual scar (scar size). Finally even if there were well defined pathologically uniform lesions infarct size could never be directly measured in patients except in those who died.

However a number of indirect indices of infarct size have been proposed for use in patients. The evaluation of ST changes from multiple leads as a blanket¹⁹ or a computerized combined signal²⁰ only indicates trends in the development of ischemia not infarct size² and is open to a multitude of theoretical objections²¹ as well as not correlating with infarct size measured by enzyme release.²² The critical importance of distinction between an effect on ischemia and on infarct size is shown by the experience with mannitol which reduced ischemia and even features of histological necrosis after 40 minutes occlusion of the coronary artery but which had no effect when given during prolonged coronary occlusion.²³

Evaluation of precordial Q waves has been proposed by Hillis and associates²⁴ and by Selawa and Shillingford.^{25, 26} In patients past the acute stage of myocardial infarction the number of abnormal Q waves on a 30 lead precordial blanket could accurately predict the extent of left ventricular dysfunction as shown by cardiac catheterization and angiography.²⁷ Askanazi and colleagues²⁸ found that the extent of early ST elevation can predict the severity of subsequent Q wave formation as judged by the extent of R wave loss. Their studies were carried out with conventional ECG leads and appear to hold promise for a simple method of assessing the effects of anti infarct agents which should decrease the eventual rate of Q formation for a given degree of early ST elevation.

The rate of release of the enzyme creatine

Myocardial infarct size Part I

Basic considerations

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The concept of infarct size has been introduced into general medical management by the studies of Braunwald, Maroko and their associates. Reduction of infarct size and protection of the ischemic myocardium have become household terms in the vocabulary of most practicing cardiologists in the United States.¹ The concept of modification of infarct size rests in part on three important observations showing that the full development of the infarct process may be measured in hours and days rather than in minutes and seconds. First, full development of the complete pathological process in animals may require several days. Secondly, experimentally produced coronary artery thrombi grow for at least 72 hours.² Thirdly, clinical observations show that reinfarction (or extension) of infarction occurs in many patients frequently after their discharge from an intensive care unit. A further complication is expansion of the infarct which occurs chiefly in large transmural and not in small subendocardial infarcts in keeping with the importance of limitation of infarct size.

Although the clinical syndrome of acute myocardial infarction will be the prime object of this review, it must be stressed that a *pathological* diagnosis of infarction can only be made in the presence of necrosis whereas a *clinical* diagnosis can frequently be made in the early hours when the actual necrotic process is still developing. Thus a more appropriate initial clinical diagnosis would be developing or impending myocardial infarction.³ This review first considers the

possible initial events in developing myocardial infarction and then the factors promoting the progression from ischemia to infarction. Thereafter the effects of therapeutic agents are considered.

One hypothesis is that during the process of development of infarction there is an imbalance between the myocardial oxygen supply and demand. Factors increasing the oxygen demand are held to worsen the ultimate infarct size. Conversely, factors improving the oxygen are held to improve the ultimate infarct size. But confusion arises from the delicate balance between salutary and harmful effects of the specific interventions. Thus, for example, reduction of the oxygen demand of the heart by reduction of the afterload also reduces the coronary perfusion pressure and the latter effect may reduce the collateral blood supply to the infarcting myocardium. At the same time the vast number of agents available to reduce infarct size has become bewildering to the average cardiologist and the principles of choice obscure.

It could legitimately be argued that infarct size reduction in patients has no place in our present state of knowledge until the results of randomized double blind studies with long term follow up become available. However, considerable endeavor has been put into animal experiments to show that infarct size reduction is possible and there has been much thought and discussion about methods of indirectly assessing ischemic injury and infarct size in man. The topic dominates many discussions at cardiological meetings. Therefore, it seems appropriate to review present knowledge of the principles involved and the chief agents being evaluated in patients. Because the specific aim of those agents is the capacity of limit infarct size, it seems appropriate to designate

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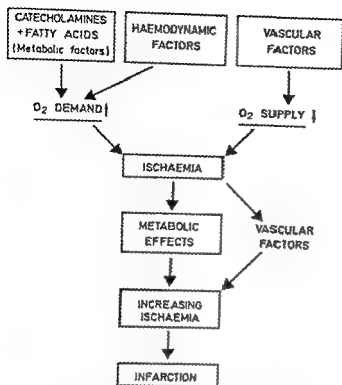


Fig 1 Ischemia can be caused by (1) a reduced oxygen supply resulting from vascular factors (see Fig 2) or (2) by an increased oxygen demand resulting from hemodynamic (see Fig 3) or metabolic factors (see Fig 4). Ischemia once produced can in turn produce metabolic changes that increase ischemic damage and eventually cause infarction (see Fig 6). Proton production may have a special role in increasing the ischemic damage (see Fig 6).

ischemia and those factors causing the transition from ischemia to infarction and to consider whether those processes are amenable to therapeutic intervention.

Initial events in acute myocardial infarction

Animal models of myocardial infarction have generally used either (1) acute occlusion by ligation of otherwise healthy coronary arteries frequently in open chested anesthetized dogs or (2) massive injections of catecholamines. The former procedure produces transmural myocardial infarction and the latter procedure produces subendocardial necrosis even when more sophisticated techniques such as the electrical production of arterial thrombi or arterial occlusion by a screw clamp, uniaxial balloon or embolization by glass balls are used and there are still many critical differences in the situation in patients with acute myocardial infarction.

The ideal model must be a subhuman primate with spontaneously occurring severe coronary

atherosclerosis superimposed thereon would be the primary event known to occur in man. That primary event still remains unknown. In those many patients with heart attacks who die within the first hours and die an arrhythmic death^{22, 23} the initial event in such deaths does not appear to be an occlusive thrombus²⁴ even when there is bradyasystolic cardiac arrest²⁵. The role for evanescent thrombi or platelet aggregations²⁶ cannot be excluded. If coronary artery spasm should play a major or even a contributory role in heart attacks²⁷ then the production of a suitable animal model becomes even more complex.

Nevertheless there is widespread recognition that very early lesions both in animals and man have a variable and possibly predominant element of reversibility (ischemia) whereas the eventual lesion is irreversible (infarction). It is therefore appropriate to concentrate first on the factors that might produce ischemia and then on those factors underlying the transition from ischemia to infarction.

Ischemia can be caused by impaired delivery of oxygen by poor blood supply as a result of vascular factors (Fig 1). Alternatively the oxygen demand can be enhanced by hemodynamic or metabolic factors and ischemia could result especially in the presence of some degree of reduced coronary flow. Metabolic factors may also act in other ways such as promotion of membrane damage. Ischemia once produced can in turn provoke metabolic and vascular changes which aggravate the ischemia and ultimately produce infarction (Fig 1). The production of ischemia by vascular, hemodynamic and metabolic factors will now be considered.

1 Role of vascular factors (Fig 2) Traditionally arterial obstruction has been the event initiating ischemia of sufficient severity to lead ultimately to acute myocardial infarction and mechanical block has been regarded as the most important cause of vascular obstruction. In addition to thrombosis, arterial obstruction may be caused by embolism, formation of platelet aggregates and by plaque rupture or by formation of a thrombus on a preexisting plaque. But the causative role of such factors especially of the thrombus is controversial. Coronary vasospasm is coming to the fore not only as a cause of angina at rest but of infarction. Little is known about the mechanism of arterial spasm. That coronary

kinase (= CK = creatine phosphokinase = CPK) has been studied extensively by Sobel's group.²⁹ The theory is that the accumulation of CK in the blood derives from the infarct provided that no intramuscular injection has been given in which case the cardiospecific isoenzyme MB CK should be used. In practice numerous problems arise including the high rate of enzyme destruction within the infarct zone and the difficulty of assessing the influence of factors altering the rate of removal of CK from the circulation.³ Nevertheless, infarct estimation by the CK method is a clinically useful procedure.³⁰ Furthermore, by making certain assumptions, the expected infarct size for any given patient can be determined from the initial CK values before the infarction and can be compared with the actual infarct size after interventions.³ Although the latter procedure is perhaps most open to theoretical objections, nevertheless it has been used to show the beneficial effect of afterload reduction³ and the harmful effects of digitalis given to patients without severe heart failure.³¹ A practical problem with this technique is the requirement for frequent blood sampling over a prolonged period.

Radionuclide techniques are particularly popular at the moment. For example, myocardial scintigraphy with 99m technetium glucoheptonate correlates well with infarct weight in dog infarcts.³² In patients who died with large myocardial infarction and who had been studied by 201 thallium during the acute phase, there was good correlation between scintigraphic and post mortem estimation of infarct size. But even by using a very sophisticated technique (¹³C palmistate of half life 20 minutes giving a cold infarct scan and quantified by positron emission tomography³³) the results are not at present accurate enough for assessing the effects of therapy.

Thus infarct size cannot be directly measured but can only be indirectly assessed by trends in the electrocardiogram by the patterns of enzyme release and possibly by radionuclide techniques. Therefore, infarct size is not only a somewhat debatable term but is difficult to measure. The term has however firmly introduced itself into modern cardiologic practice.

Hereafter the term *infarct size as applied to patients will be taken to refer to such indices of infarct size rather than to accurately measured infarct size*.

Differentiation between ischemia and infarction

In the original and classic paper by Maroko, Braunwald and co-workers, the extent and severity of epicardial ST segment elevation 15 minutes after coronary artery ligation in the dog could be used as a predictor of the severity of myocardial cellular damage 24 hours later as assessed either by histologic damage or by the extent of depletion of the enzyme creatine kinase (= creatine phosphokinase). It was reasoned that any increase in the degree of enzyme loss and histologic damage must indicate that the ultimate infarct was bigger and thus infarct size had increased, although the latter was never quantified in a precise pathologic sense. The Braunwald group thereafter meticulously measured both ST elevation and enzyme depletion before concluding that a variety of agents altered infarct size. Other investigators using the same model sometimes measured the ST elevation at 15 minutes and omitted the enzyme and histologic data. In patients it was a small step towards equating effects on precordial ST elevation with effects on infarct size. Although there is a relation between early ST elevation and later QRS changes, it must be understood that ST elevation is an index of acute ischemic injury provided that other causes are excluded, whereas it is the loss of II wave and formation of the Q wave that more closely corresponds to coagulation necrosis in infarction. The difference between *ischemia* and *infarction* is that the former is a reversible decrease in blood flow severe enough to have metabolic consequences such as depletion of ATP and anaerobic metabolism—the latter is the irreversible development of tissue necrosis.

Logically, efforts to limit infarct size in patients would therefore be aimed at (1) countering the initial event causing ischemia and (2) countering those events causing the progression from ischemia to infarction, while (3) in no way impeding the process of wound healing and scar formation. Furthermore, the effects of any such therapeutic procedure should be capable of assessment by a clinically feasible method of measuring infarct size. But infarct size cannot be assessed with complete confidence nor has its reduction yet been shown to be beneficial to the patient. Assuming that evidence will be forthcoming on the effect of limitation of infarct size in patients, it becomes logical to examine the production of

INFARCTING HEART

O₂ BALANCE

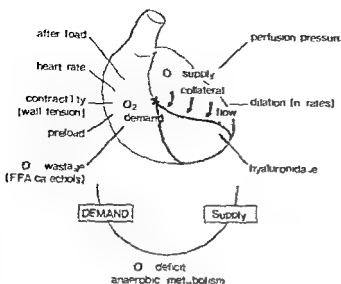


Fig 3 Hemodynamic factors of importance in the genesis of ischemia. In regional ischemia (infarcting myocardium) there is a balance between the oxygen demand and the oxygen supply. The oxygen demand exceeds the oxygen supply and there is an energy deficit. The oxygen demand depends largely on the contractility of the heart, the heart rate and the afterload but metabolic factors may play an important role. "Oxygen wastage" refers to those metabolic processes which impair the conversion of oxygen taken up to ATP available for contractile purposes. The oxygen supply depends largely on the collateral flow which in turn depends on the difference between the coronary perfusion pressure and the intramyocardial pressure, and the degree of coronary vasodilation (which may be possible by increased use of nitrate). It is also possible that hyaluronidase increases the permeation of nutrients brought to the infarcting tissue by the collateral flow. (Reproduced by permission of Postgraduate Medical Journal.)

restoration of normal blood flow to the ischemic zone whether surgically or by reversal of experimental occlusion would inevitably bring about an improvement. Indeed that assumption underlines the recommendation of a recent panel that acute coronary occlusion should be treated aggressively by coronary bypass as soon as possible and within 4 hours of the event.³ However reperfusion after 30 minutes of experimental coronary ligation actually accelerates ischemic damage³⁴ and in *per se* promotes calcium uptake³⁵ with harmful effects on mitochondria.³⁶ After 90 minutes of severe ischemia this capacity for calcium uptake by mitochondria is lost presumably because of the severity of mitochondrial damage³⁴ and it is presumably safer to reperfuse how the situation in patients with infarction with varying degrees of coronary

occlusion variable collateral circulation and possibly the further complication of arterial spasm cannot readily be assessed. The occurrence of contraction band necrosis following coronary artery bypass graft surgery may reflect reperfusion damage. It would seem prudent to bear in mind that reperfusion may be harmful especially in the early phases of ischemic damage while late reperfusion may not be successful.

Once ischemia has developed a further series of events (summarized in Figs 2 and 4) can be provoked to produce increasing ischemia and ultimate infarction.

2 Role of hemodynamic factors (Fig 3) The hemodynamic factors controlling the oxygen uptake of the heart are well established³⁷ and include the afterload (approximately represented by the arterial systolic pressure) the heart rate and the contractility of the heart. The preload plays a lesser role because volume work is not as energy requiring as pressure work.³⁸ However an increased preload could further dilate a failing myocardium thereby increasing the wall tension and hence the oxygen demand. It is proposed that these factors could (1) produce ischemia in the presence of a compromised blood supply and (2) promote the transition from ischemia to infarction and increase infarct size.³

That such hemodynamic factors can influence the myocardial oxygen uptake is firmly established. That they could influence the progression from ischemia to infarction depends on the hypothesis that there is a balance between the oxygen supply and demand of the ischemic zone (Fig 3) which can be tipped in either direction with consequent sparing or increased injury to the critically jeopardized or vulnerable cells and their ultimate survival or necrosis. This point of view calls for (1) the existence of a zone of intermediate blood supply (2) a collateral blood supply to the severely ischemic tissue and (3) the persistence of some contractile activity in ischemic tissue. The existence of tissue with these intermediate properties has been held to constitute a border zone. Moving inward from the visible edge of the cyanotic area produced by coronary artery ligation severe and progressive derangements of metabolism flow and electrocardiographic changes have been found (see also reference of Hearse and colleagues³⁹). The ischemic tissue and the border zone in the dog also retain some contractile properties.⁴⁰ In the

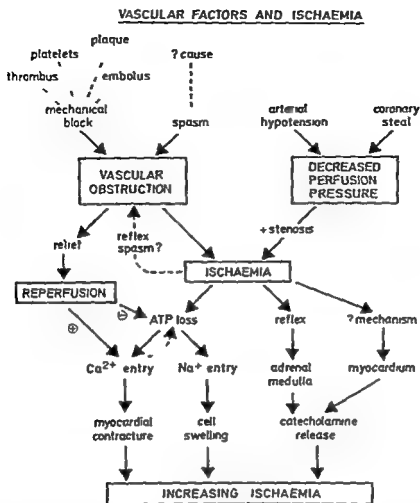


Fig 2 The classical cause of ischemia is vascular obstruction caused by a mechanical block, the latter in turn generally resulting from a thrombus. However coronary artery spasm may also play a role. Either by lysis of the thrombus or by relief of spasm reperfusion may take place with decreased loss of ATP (improved oxygenation) but increased entry of calcium which can aggravate ATP loss. Ca^{2+} entry is held to be causative in the development of ischemic contracture which increases ischemia. Ischemia can also provoke cell swelling and/or catecholamine release which also increase the severity of ischemia. A decreased coronary perfusion pressure especially in the presence of coronary artery stenosis may be another theoretical cause of ischemia.

occlusion could cause reflex vasospasm through an adrenergic mechanism was suggested by Grayson and colleagues: although their method of measuring coronary flow has now been superseded.

Experimentally the degree of collateral circulation influences the extent and severity of the infarction process in the presence of a well developed collateral circulation coronary occlusion may have no effects. Much attention has been paid to the possibility that part of the beneficial effect of nitrates in decreasing the severity of ischemia could be by augmentation of collateral flow in animals with either acute coro-

nary occlusion or chronic coronary narrowing.³⁰ In patients collaterals would be required to deliver the therapeutic agent to the ischemic zone which could explain why Gold and associates¹ found a beneficial effect of propranolol especially in those patients with angiographically demonstrable collateral vessels. Theoretically the presence of collaterals should limit the severity of infarction in man although Baroldi and Scomazzoni³² have argued to the contrary on the basis of postmortem dissection and case analysis of the coronary circulation in man. However they did not quantify the size of the collateral circulation. It might be supposed that the size of the collateral circulation

CATECHOLAMINES & ISCHAEMIC INJURY

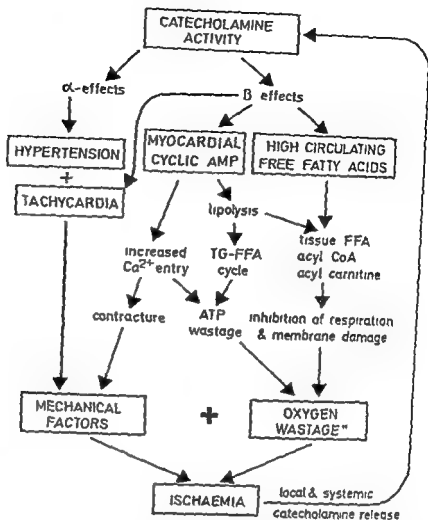


Fig 4 Catecholamines can increase ischemic injury by (1) mechanical factors such as hypertension (chiefly an α -effect) and/or tachycardia (chiefly a β -effect) (2) promotion of ischemic contracture with decreased blood flow as a result of increased calcium entry and (3) metabolic effects. The latter include the effects of increased circulating free fatty acids and increased cardiac lipolysis which may cause (1) metabolically futile cycles such as the postulated triglyceride free fatty acid (see Opie) and (2) accumulation of tissue lipid metabolites. These lipid changes lead to oxygen wastage (Section 2 of this report) through mechanisms not yet well defined. Once ischemia is established generalized or localized release of catecholamines can lead to further catecholamine activity and a metabolic vicious circle. TG = triglyceride FFA = free fatty acid Acyl CoA = long-chain acyl CoA eg. palmityl CoA

intracellular passage of a macromolecule horse radish peroxidase. An effect on cell permeability may explain why low doses of noradrenaline could induce enzyme release from the isolated heart even in the absence of major loss of high energy phosphate compounds although it remains true that high doses of catecholamines cause substantial depletion of energy as first pointed out by Fleckenstein.

The effect of catecholamines on lipolysis warrants further consideration. The myocardial

oxygen consumption in a catecholamine stimulated heart can be reduced by about 30% by an antilipolytic agent. When the metabolic "oxygen wastage" caused by noradrenaline is inhibited by an antilipolytic agent then ST segments over the ischemic myocardium fall rather than rise. Furthermore when an inotropic stimulus equivalent to that of isoprenaline is applied to the ischemic heart by glucagon or by calcium then there is less epicardial ST segment elevation. Dopamine is also a fatty acid mobilizing agent.

chemic zone flow must be reduced to zero before oxidative metabolism ceases" hence the demonstration of at least some collateral flow in animal models⁴³⁻⁴⁷ and in some patients with acute myocardial infarction⁴⁸ supports the oxygen balance theory. The existence of a clearly defined border zone albeit narrow implies that therapeutic salvage of that zone could decrease the ultimate infarct size by between 35% and 60%. These are rough calculations but give an idea of magnitude.⁴¹

However the oxygen imbalance hypothesis can be criticized. Chance's group⁴⁹ has argued that the gradients for oxygen are very steep and that mitochondria respond to oxygen in an all or none fashion thus the oxygen border zone is extremely narrow. Furthermore 24 hours after coronary ligation the border as defined by measurements of tissue creatine kinase is narrow and consists of a mixture of normal and abnormal cells. Such arguments can be countered. Thus even the Chance model allows for the existence of an intermediate cell⁵⁰ and the absence of a border zone at 24 hours does not exclude one at 25 minutes. Nevertheless it must be noted that the border zone concept has been challenged.

A major criticism of the oxygen supply versus demand theory is that in very few studies if any have both the oxygen uptake and the infarct size been measured under the influence of a therapeutic agent. And even if the overall myocardial oxygen uptake were known that does not necessarily reflect changes in a similar direction in the critical oxygen uptake of the border zone. However on the whole agents which theoretically change the myocardial oxygen uptake have subsequently been shown to change the infarct size in a similar direction.¹

3 Role of catecholamines (Fig. 4) Reab and associates⁵¹ made the basic observation that the infusion of catecholamines could precipitate features of regional ischemia in an experimental preparation with compromised coronary circulation. Since then much evidence has supported the concept that catecholamines can exaggerate the degree of myocardial ischemia although dose effects and the relative balance between α and β effects cause complex results.² Thus pure β stimulation by isoprenaline increases ischemic injury⁵² and infarct size in dogs, whereas combined α and β stimulation by noradrenaline decreased the extent of ischemic injury presum-

ably because the beneficial effects of an increased coronary perfusion pressure outweighed the harmful effect of an increased afterload⁵³ or because other unspecified beneficial effects could be achieved by low doses of noradrenaline in the absence of systemic hypertension⁵⁴ and despite elevation of circulating free fatty acids.⁵⁵ But it must not be assumed that α -effects are necessarily beneficial. Methoxamine given in similar doses decreased infarct size in one series⁵⁶ and exaggerated ischemic injury in another.⁵⁷ These effects of dosage and of comparative stimulation of α and β receptors are not yet well understood.

β -effects of catecholamines appear to be harmful to the ischemic myocardium and the mechanisms involved may include (1) an increased heart rate⁵⁸ (2) increased circulating free fatty acids⁵⁹ and (3) the effects of an increased intracellular cyclic AMP level. Cyclic AMP is fundamentally involved with the entry of calcium ions into myocardial cells.⁶⁰ Increased entry of calcium ions could in part explain the phenomenon of oxygen wastage found in a classical study by Lovatt Evans.⁶¹ Uptake of calcium by mitochondria is energy requiring and occurs as an alternative to oxidative phosphorylation.⁶² Increased calcium entry may also be harmful by provoking myocardial contracture with compression of the blood supply. Another postulated mechanism whereby cyclic AMP in excess could harm the heart is by stimulation of lipolysis in the heart: the resultant liberation of long chain free fatty acid could in the presence of a glycerophosphate derived from glycolysis promote re-esterification of fatty acid to triglyceride with the operation of a triglyceride-fatty acid cycle⁶³ which is energy wasting.

Yet another mechanism to produce oxygen wastage could be by accumulation of products of fatty acid metabolism in the tissue (tissue free fatty acid acyl CoA and acyl carnitine) these compounds can inhibit respiration⁶⁴ and cause membrane damage. Even if oxygen does reach the ischemic mitochondria it need not be efficiently used. Thus there are problems not only with the oxygen supply but also with the conversion of the available oxygen to energy.

Besides mechanical factors and oxygen wastage catecholamines may also act by increasing cell permeability which occurs within 10 minutes of the exposure of the healthy animal heart to high doses of catecholamines as evidenced by the

cholamines on the infarction process Isoproterenol (0.25 to 0.50 $\mu\text{g/kg}$ /minute) increases depletion of myocardial creatine kinase an indirect marker of the extent of necrosis¹ there is enzyme depletion in those sites which are not involved by coronary occlusion alone—i.e. the infarct has extended. The dose of isoproterenol is similar to the estimated rate of secretion of catecholamines in patients with acute myocardial infarction²². Even spontaneous rates of secretion of adrenaline after coronary ligation in dogs are able to promote damage away from the ischemic zone as shown by histochemical changes²³. In the isolated rat heart noradrenaline 10⁻⁶ M or higher is able to induce ultrastructural changes including hypercontracted cells²⁴ a type of lesion found especially around the edge of the human infarcts¹ and presumably also the result of catecholamine secretion.

In high doses catecholamines can produce large scale infarct like necrosis even in the total absence of coronary arterial narrowing²⁵. Whether such massive doses of catecholamines could ever be secreted in response to extreme stress or other factors and hence account for some cases of infarction occurring without coronary artery disease is a matter of speculation.

If however catecholamines can initiate or extend ischemic injury and ischemic injury can provoke release of catecholamines then a harmful vicious circle would be set up (Fig. 4).

Progression from ischemia to infarction (Fig. 5)

At a cellular level the harmful effects of ischemia are a combination of (1) poor oxygen delivery leading to depressed mitochondrial production of ATP and an accumulation of fatty acid metabolites and (2) poor washout of lactate protons and carbon dioxide which can all contribute to the severity of ischemic damage.

1 Effects of poor oxygen delivery From the clinical point of view large scale enzyme release from the heart is virtually synonymous with cell necrosis—i.e. myocardial infarction as opposed to other chest pain syndromes hence it would be useful to establish which metabolic events underlie the liberation of enzymes from the heart. In a number of simpler models ATP depletion can be related to the extent of enzyme release. Thus the extent of fall of tissue ATP in the perfused anoxic dog heart correlates very well with the amount of

enzyme released. However in regional ischemia (developing experimental myocardial infarction) substantial tissue depletion of ATP can occur 15 minutes after ligation before the tissue creatine kinase had decreased²⁶. More probably may be a subcompartment of ATP more readily accessible to the cell membrane which has a special role in the maintenance of cell membrane integrity as argued by Bricknell and Opie²⁷. ATP is produced by glycolysis and the evidence for the role of ATP in another membrane associated event namely the production of the normal action potential. Thus increased provision of glycolytic ATP may be one way whereby glucose is a favorable fuel for the infarcting myocardium than is fatty acid.

The observation that glucose decreased and free fatty acid increased enzyme release from the coronary ligated rat heart²⁸ is consonant with the above hypothesis but by no means provides definitive evidence. In fact the beneficial effects of glucose and the harmful effects of fatty acids are extremely complex. In severely ischemic tissue the rate of glucose uptake and glycolysis is inhibited by the severity of the ischemia²⁹ hence the above relationship probably holds only for mildly or moderately ischemic tissue and not for severely ischemic tissue.

The mechanism of fatty acid toxicity includes the intracellular accumulation of free fatty acid³⁰ acyl CoA³¹ acyl carnitine³² and lysophospholipid³³. Early work stressed the possibility that accumulation of free fatty acid in tissue (secondary to impaired oxidation) could cause uncoupling and thereby oxygen wastage; more recently accumulation of the activated fatty acid metabolite long-chain acyl CoA has been found and emphasized as a cause of impaired utilization of oxygen so that transfer of ADP into the mitochondria is blocked as transfer of ATP outwards³⁴. However acyl CoA accumulation should depress mitochondrial oxygen uptake whereas it is usually oxygen wastage which is held to be an effect of excessive provision of fatty acids during ischemia (Opie³⁵).

Of the other effects of fatty acid metabolism those on the membrane are a rather nonspecific but nevertheless important effect which can contribute to lysosomal activation (see later). Inhibition of the membrane ATPase (Na⁺/K⁺)

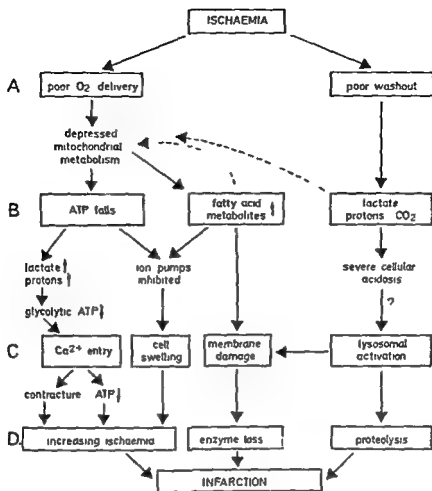


Fig 5 Proposed metabolic mechanisms whereby ischemia can produce infarction. Panel A shows the two major effects of ischemia namely poor O₂ delivery and poor washout of metabolites. Panel B proposes that depressed mitochondrial metabolism results in decreased production of ATP and accumulation of fatty acid metabolites (see Fig 4) which are normally metabolized in the mitochondria. Anaerobic metabolism causes accumulation of lactate and protons (the latter from breakdown of ATP) and continued residual respiration causes accumulation of CO₂. Panel C proposes that decreased production of glycolytic ATP (a result of accumulation of lactate and/or protons) results in increased calcium entry. Inhibition of ion pumps by lack of ATP and by inhibition of fatty acid metabolites results in sodium and water retention and cell swelling. Fatty acid metabolites also probably cause membrane damage which may also result from lysosomal activation as a result of a severe cellular acidosis or possibly as a result of other mechanisms such as ATP depletion.²⁰ Panel D proposes that the final events leading up to infarction may be increasing ischemia caused by ischemic contracture and cell swelling, enzyme loss from membrane damage and proteolysis from lysosomal activation.²¹

and increases ischemic injury more than an equivalent inotropic response obtained by calcium. That oxygen wastage may exaggerate the effects of ischemia in man is suggested by the finding that in patients with coronary artery disease increased fatty acid uptake accounts for half of the increase of myocardial oxygen uptake which results from catecholamine stimulation the other half being due to tachycardia.

In patients with acute myocardial infarction plasma catecholamine values are about 1 to 10

μg/L plasma (see Vetter and colleagues²⁰). Such concentrations greatly increase ischemic damage in isolated rat hearts. The cause of the increased catecholamine concentrations is not clear but may include psychological stress (see Opie²¹) and reflexes originating in the border zone of the infarcting tissue.²²

The data reviewed thus far indicate complex effects of catecholamine stimulation on ischemic injury with the majority of effects being harmful. Less work has been done on the effects of cate

before there is total depletion of energy. Once taken up, calcium can accumulate in the mitochondria and can contribute to the development of ischemic contracture, usually an irreversible event.⁵⁴ More direct evidence for the postulated role of calcium in irreversibility has been obtained with a lanthanum probe. Lanthanum is a trivalent ion with properties resembling those of calcium but not normally found within the cell. With progressive hypoxia of the cat papillary muscle, lanthanum can be found at intracellular sites of high calcium affinity as ultrastructural changes develop after 2 to 3 hours of hypoxia.¹⁰⁶

However, in experimental infarcts in dogs it is doubtful that massive calcium uptake is the critical event accompanying or causing irreversibility, because (1) scans for ^{99m}Tc technetium stannous pyrophosphate are negative 7 hours after occlusion but strongly positive after transient occlusion;¹⁰⁷ (2) uptake when found is especially localized to the border rather than to the central zone of the infarct¹⁰⁸ and (3) the uptake of the label does not appear to be directly related to the severity of necrosis.¹ The effectiveness of calcium antagonist drugs in reducing the size of experimental infarcts¹⁰⁹ also does not prove the role of calcium in the pathogenesis of infarction because such drugs have multiple effects including for example relaxation of the coronary arteries.

In patients, increased calcium uptake does not appear to occur very soon after the induction of ischemia by coronary vasospasm as shown by the fall rather than the rise of dp/dt max in patients during an episode of ST elevation. Nevertheless, increased calcium entry may be an important initial event in the pathogenesis of other types of myocardial ischemia as suggested by Harris.⁶

Thus, although increased uptake of calcium into the heart cell is generally held to be an adverse effect of ischemia and could help to promote or cause permanent damage especially after reperfusion, yet the evidence incriminating calcium is not yet firm and the use of calcium antagonist drugs is still in the early stages of investigation.

2 Effect of poor washout. There are major metabolic differences between hypoxia with maintained cell perfusion (eg depriving a perfused heart of its oxygen supply) and ischemia (with poor washout plus metabolite accumulation). The classic effect of poor washout is the

accumulation of protons (Fig 6) for example from anaerobic glycolysis with ATP breakdown or from a variety of metabolic cycles which can also produce protons.⁸ Although severe acidosis must be harmful to the cell, some evidence¹¹¹ suggests that milder acidosis can protect the hypoxic cell by keeping out calcium (protons and calcium ions can compete for superficial binding sites).

Less well publicized are the effects of accumulation of other metabolites. Thus retention of carbon dioxide partially as the result of continued residual respiration¹¹² may contribute to impaired contractile activity soon after coronary artery ligation.¹¹³ Lactate accumulation may help inhibit glycolytic flux¹¹⁴ and thereby minimize the beneficial effect of provision of glucose in zones of severe ischemia. Lactate may also contribute to mitochondrial damage and may shorten the action potential duration.¹¹⁵ Finally, accumulation of NADH in the mitochondria and cytoplasm as an effect of impaired oxidative metabolism will depress citrate cycle activity¹¹⁶ and impair the capacity to use such oxygen as is available. This mechanism together with mitochondrial depression induced by acyl CoA could explain why the cell can undergo metabolic deterioration even though oxygen may still be reaching the infarcting tissue by collaterals.⁴

A cogent hypothesis linking accumulation of metabolites with cell death is the lysosomal hypothesis, according to which ischemia causes accumulation of protons and of membrane active fatty acids which in turn reduces membrane integrity including that of the lysosomes. Thereafter lysosomal enzymes leak out,¹¹⁷ cellular constituents including critical components of the cell membranes are attacked by these lysosomal enzymes and cell necrosis is initiated or accelerated.¹¹⁸ Although it cannot be stated with certainty that lysosomal changes are the cause and not the result of a critical stage in myocardial cellular damage, yet there is a coincidence in time between lysosomal activation and the appearance of ultrastructural changes of irreversibility. Further weight is given to the lysosomal hypothesis by the effects of methylprednisolone and d-glucose in stabilizing lysosomes and in reducing ischemic or hypoxic damage in a variety of models.¹¹⁹ At present the side effects of these agents in impairing wound healing limit their testing in man, but the possibility of new analogs without

PROTON PRODUCTION IN ISCHAEMIA

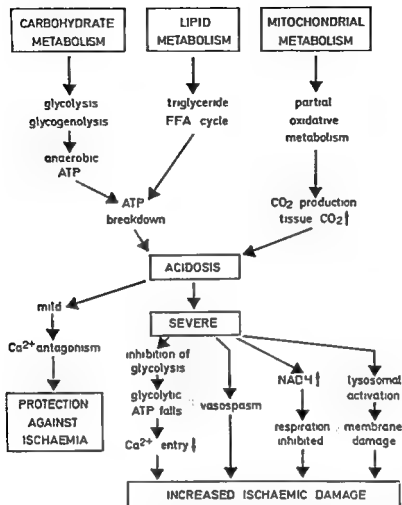


Fig 1 During ischemia protons can be produced as result of carbohydrate or lipid metabolism or mitochondrial respiration. The mechanisms involved are (1) activation of glycolysis with production of anaerobic ATP and (?) activation of triglyceride breakdown with simultaneous incorporation of free fatty acids (FFA) into triglyceride—i.e. the triglyceride FFA cycle. In either case breakdown of ATP occurs and protons are liberated. An increased tissue pCO_2 resultant from partial oxidative metabolism can together with protons formed from ATP breakdown cause an intracellular acidosis. If mild the acidosis may protect from ischemia by calcium antagonism but if severe increased ischemic damage may result by (1) inhibition of glycolysis and decreased calcium entry (2) acidosis-caused vasospasm (3) inhibition of mitochondrial respiration by NADH and (4) lysosomal activation.

can be achieved by low concentrations of acyl carnitine which also accumulates in ischemia. These membrane effects may together with early loss of ATP explain the rapid potassium loss after coronary ligation.

Loss of potassium and gain of sodium can be detected within minutes of coronary ligation by coronary venous changes but significant tissue depletion of potassium takes hours to develop. Associated with sodium retention is edema formation recently stressed as a cause of the no reflow

phenomenon whereby increased swelling of myocardial cells can impinge on the vascular bed and diminish blood flow even if reperfusion were achieved by release of coronary occlusion.

A further working hypothesis is that ATP is required for the activity of those ionic pumps which maintain the cellular balance of calcium ions. Calcium accumulates in cells damaged by ischemia especially after reperfusion. The uptake of calcium by mitochondria is energy wasting and must be occurring in the pre-necrotic phase

20 and 40 minutes. From these points of view, it is of interest that 8 hours post ligation the central infarct zone has an ATP value of below 1 $\mu\text{moles/g}$ with severe depletion of total adenine nucleotide and of glycogen, but the infarct edge has values of 120 to 18 $\mu\text{moles/g}$ and the peri infarct zone has values of 2 to 3 $\mu\text{moles/g}$ and the glycogen is near normal. These indirect arguments suggest that by 6 hours only the peri infarct tissue and perhaps some of the infarct edge is potentially salvable. Other information shows^{1,7} that 1 to 4 hours after acute coronary ligation in dogs, epicardial ATP even in the central infarct zone is still dropping to the critical levels. Four hours post ligation the endocardial zone has developed changes in the K⁺/Na⁺ ratio compatible with necrosis with the appearance of mitochondrial dense bodies whereas the epicardial zone has much milder changes and still constitutes a border zone.^{1,8}

Although indirect evidence links the severity of ATP depletion to irreversibility major reservations are (1) in some situations it is loss of production of glycolytic ATP and not the severity of over all cellular ATP depletion that can be related to the severity of ischemic injury^{1,9} (2) ATP depletion may merely be a nonspecific index of cell damage and other cellular events^{1,9} such as glycogen depletion or potassium sodium changes or activation of lysosomal enzymes¹¹⁷ can also be circumstantially linked to the onset of necrosis. Thus the severity of ATP depletion should be viewed only as an index of the severity of ischemic damage. The very complex events surrounding the onset of necrosis remain imperfectly understood.

Taking into account the evidence based on rates of ATP depletion⁷ ionic changes^{9,11} glycogen depletion^{1,10} mitochondrial calcium uptake¹¹ lysosomal activation (see references to Figs 5 and 6) the commencement and pattern of cardiospecific enzyme release^{12,13} and the rate of onset of Q wave formation¹⁴ it is reasonable to conclude that (1) *early irreversible damage* starts about 20 to 40 minutes after complete coronary occlusion in animals and within 2 hours of the onset of symptoms in patients (2) *irreversibility progresses* over a period of several hours as judged by the rate of progression of cellular metabolic changes and enzyme release and Q wave formation and (3) there is therefore a perceptible period of several hours duration dur-

ing which *therapeutic intervention* can be attempted.

Basic considerations conclusions

Factors concerned with the initiation of ischemic injury and the progression of such injury to infarction are (1) vascular factors including the role of the controversial thrombus (2) hemodynamic factors including the hypothesis that there is a balance between the oxygen supply and demand in the ischemic zone and (3) catecholamine activity, which is generally harmful to the developing infarct, although there are important dose effects and complexities introduced by the relative effects of α and β stimulation. The cellular events concerned with the change from ischemia to infarction include ATP depletion, accumulation of fatty acid and acyl CoA alterations in ions including calcium the retention of metabolites (protons carbon dioxide and lactate) and lysosomal activation.

There is an important difference between *ischemia* a reversible event and *necrosis* or *infarction* which is irreversible. Experimentally a decreased blood supply or increased hemodynamically induced oxygen demand or increased catecholamine activity can worsen the severity of the ischemic process and the extent of the ultimate infarction. However the difficulty in assessing infarct size even in experimental preparations has led to the use of indirect indices of necrosis (ECG changes tissue enzyme depletion). The existence of a border zone and of cells of intermediate metabolic characteristics (neither totally healthy nor dead) for anti infarct agents to act on seems probable but by no means proven. A general metabolic response further alters the metabolic patterns in the ischemic zones.

A consideration of the time scale involved suggest that therapeutic intervention could be justified for at least some hours post coronary ligation or after the onset of symptoms in patients. However in most severely ischemic zones irreversibility would already have set in by 20 to 40 minutes after complete coronary occlusion.

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an effect on wound healing suggests that membrane stabilization will eventually be tested clinically

Role of general metabolic response in acute myocardial infarction (Fig 7)

In addition to the above events (chiefly described in experimental animals) there is in patients the development of a general metabolic response associated with acute myocardial infarction.^{1,2} The major components are glucose intolerance^{1,2} increased catecholamine secretion and raised blood free fatty acids.³ Each of these changes could contribute to the progression of ischemic damage (Fig 7) and the catecholamine and fatty acid changes could contribute to the development of arrhythmias (see Opie⁷)

Time scale for irreversibility

When does irreversibility set in? Data based on the response to reperfusion after coronary ligation or global ischemia are not necessarily reliable because (1) reperfusion hastens the development of ischemic damage⁴ and (2) ischemic damage has a graded and not a global effect depending on the extent of the collateral flow. Thus the point of no return must be defined for regional ischemia without reperfusion. From the metabolic point of view the changes that have been emphasized in this review are the transition from ischemia to infarction with a fall of ATP, increased fatty acid metabolites and the accumulation of lactate, protons and CO₂ with a severe intracellular acidosis (Fig 5) with further limitation of flow from edema formation and Ca²⁺ contractures. Limited information is available about the time scale of such changes in experimental myocardial infarction. Over the period 1 to 4 hours post ligation lactate no longer rises (probably because of continued washout by collateral flow) and the pH change is slight but there is progressive depletion of ATP⁵ not so much in the central zone but in the border zones.⁶ Substantial accumulation of fatty acid metabolites probably occurs within one hour.⁶ Of the major metabolic changes it may be progressive depletion of adenosine triphosphate that becomes critical.

On theoretical grounds Kubler and Spieckermann¹⁰ proposed that when the ATP decreases to 2 $\mu\text{M/g}$ (33% of control) no recovery from severe global ischemia can occur. Jennings and

GENERAL METABOLIC RESPONSE

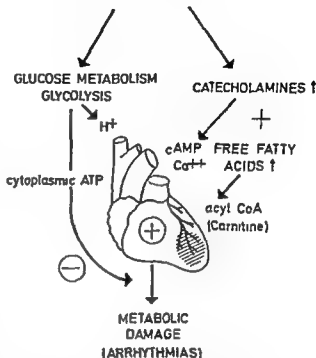


Fig 7 Schematic representation of effects of general metabolic response in acute myocardial infarction on the severity of metabolic damage and the development of arrhythmias. The general metabolic response includes glucose intolerance, increased catecholamines and high blood free fatty acids.^{1,2} These general metabolic changes can increase metabolic damage (indicated by + sign) and possibly help provoke arrhythmias. Catecholamines may exert an effect at a cellular level by cyclic AMP, calcium changes and by mobilizing free fatty acids (see Fig 4). Free fatty acids may act by intracellular accumulation of acyl CoA: carnitine has an important role in the transport of acyl CoA into mitochondria.¹⁰ Increased glycolysis can be induced therapeutically by administration of glucose and insulin. In severely ischemic tissue protons (H⁺) accumulate and are derived from ATP produced by glycolytic flux. Protons do not accumulate to the same extent in moderately ischemic cells because the predominant pattern of metabolism is still oxidative.¹¹ In moderate ischemia, increased production of cytoplasmic ATP by promotion of glycolysis may speculatively inhibit the extent of metabolic damage.¹⁰ Several agents promoting metabolic damage may also in specified conditions provoke arrhythmias and some antiarrhythmic agents may lessen the extent of ischemic damage (see Section 2 of this report). (Based on Brucknell and Opie⁷ by permission of the University Park Press.)

co workers¹² find that in severely ischemic posterior papillary muscle preparations in which collateral blood flow is less than 10% of control the critical ATP is about 20% of normal—i.e. about 1.2 $\mu\text{M/g}$ and the critical survival time is between

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and the late rightward forces do not reach one millivolt in magnitude the likely choice is posterobasal infarction. Further caution must be applied in this situation as anterior fascicular delay may be present in the complete absence of coronary disease or infarction.

In a very recent study echocardiography proved to be a highly useful discriminant in identifying patients with dilated right ventricles or with hypokinetic posterior left ventricular walls enabling better separation of RVH from posterobasal infarct cases than was possible from vectorcardiographic considerations alone.⁹

Left ventricular hypertrophy and pseudo infarction

The posterior QRS addition to QRS voltage which occurs in left ventricular hypertrophy may mimic anterior myocardial infarction.^{117, 145, 158} Early posterior addition may reduce the duration and magnitude of the normal early anterior forces to very low values or to zero. In addition advanced LVH as described previously, may in its most advanced form result in a clockwise horizontal loop.^{11, 49} Thus the picture of extensive anterior infarction may be closely mimicked. Several authors have studied this problem and all agree that the usual diagnostic criteria for anterior infarction are much less sensitive in the presence of left ventricular hypertrophy especially when this is the result of aortic valve disease.^{1, 141, 15} Therefore when the vectorcardiographer reviews a horizontal QRS loop lacking anterior forces and presenting with marked posterior orientation and even with clockwise rotation he should suspect a pseudo infarction if the QRS voltage is high suggesting concomitant left ventricular hypertrophy.

Unfortunately neither the direction nor the rotational characteristics of the T loops in these cases serve as a useful discriminant between severe left ventricular hypertrophy and LVH accompanied by anterior infarction.^{66, 2}

Uncommonly the frontal loop in severe left ventricular hypertrophy may mimic inferior myocardial infarction with an upward bowing of the first half of the QRS loop which may remain superior for 30 msec thus mimicking a diaphragmatic infarct.¹ These loops are probably somewhat more common when the left ventricular hypertrophy is the basis of aortic insufficiency than aortic stenosis although both lesions may

result in a pseudo inferior infarction picture.

Cardiomyopathies of various etiologies may mimic myocardial infarction vectorcardiographically.^{140, 142, 143, 146, 154} The markedly hypertrophied intraventricular septum seen in hypertrophic subaortic stenosis is believed to be responsible for the marked initial rightward anterior forces which may occur in that condition and which may mimic dorsal or lateral infarction.

However at least one study denies that any significant difference exists between the left ventricular hypertrophy patterns resulting from aortic stenosis, aortic insufficiency or hypertrophic cardiomyopathy.⁴⁴

Certainly the myocardial deposits or scars which occur in infiltrative cardiomyopathies such as sarcoidosis or amyloid disease may result in QRS loop deformities and bites which are indistinguishable from those seen in coronary disease and myocardial infarction.^{11, 111, 112}

The congestive cardiomyopathies may present with a wide variety of vectorcardiographic abnormalities particularly conduction disorders including hemiblocks and simple axis shifts.¹ However in many such cases mimicry of myocardial infarction in any location occurs.

In cardiomyopathies the combination of conduction disturbance, small areas of fibrosis and left ventricular hypertrophy can readily lead to distortions of the activation sequence leading to QRS loop deformities readily mistaken for those of myocardial infarction. An interesting variant is seen in the mitral valve prolapse syndrome in which coronary disease is absent but myocardial contractile abnormality is frequently present. Although the QRS loops in these patients are commonly normal an occasional patient will present with complete absence of anterior forces resembling anterior myocardial infarction.

Another variety of cardiomyopathy which presents a rather typical pseudo infarction pattern is Duchenne's muscular dystrophy in which pathological changes occur in the posterobasal wall of the left ventricle.¹⁰ As might be expected this results in an anterior displacement of the QRS loop which thus could be misinterpreted as true posterior infarction.

The pre-excitation (WPW) syndrome in which initial QRS activation may be directed markedly anterior, posterior or superior and thus may mimic anterior, posterior or inferior infarction will be discussed in a separate section.

Fundamentals of clinical cardiology

Clinical vectorcardiography in adults Part 2

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Pulmonary emphysema and pseudo anterior infarction

The effects of emphysema on the distribution of QRS forces on the torso surface has been mentioned previously in this review. The resultant decrease in anterior QRS forces which may be simulated by experimental overinflation of the lungs may result in a scalar ECG and a vectorcardiogram resembling anterior myocardial infarction owing to the poor progression of scalar precordial R waves and the minute duration and magnitude of anterior forces recorded. Watanabe and associates¹ have studied this problem using computer techniques and multivariate statistical analysis. Four vectorcardiographic measurements were selected to enable the best discrimination between these two conditions. The location of the 15 msec vector in Lead Z (anterior or posterior) was one useful criterion. The mean value for anterior duration was 30 msec in the emphysema group but only 14 msec in the anterior infarction group. The authors found that 25 msec provided a good discriminating point. The second criterion used was the ratio of the rightward forces (S_x) divided by the sum of the leftward plus rightward forces ($R_x + S_x$). This value was 0.417 in the chronic obstructive lung disease group and 0.245 in the anterior infarction group—indicating a greater relative strength of rightward voltage in the emphysema patients.

The third criterion which separates the groups was the simple voltage summation of $R_x + R_z$

(leftwards plus posterior forces). This value was 0.85 in the emphysema group but 1.6 in the anterior infarction group. Finally, the total QRS duration was a fourth useful discriminator with a mean value of 93 msec in the emphysema group and 105 msec in the myocardial infarction group. Despite the use of these criteria the greatest difficulties are encountered in patients with emphysema whose anterior forces are completely absent. This may occur although infrequently in the absence of coronary disease or myocardial infarction and it poses a sometimes impossible differential diagnosis.

Although considerable overlap was encountered by all investigators who have approached this problem it seems apparent that the use of multiple criteria rather than any single one is best in attempting to separate the two conditions. Mitral stenosis which often results in a small posteriorly oriented QRS loop with terminal forces oriented to the right may also present difficulties in discrimination against anterior infarction.²⁻⁴ Fortunately clinical features and the age and sex of the patients are frequently very valuable in making a preliminary differentiation in mitral stenosis whereas the patients with chronic obstructive lung disease are often clinically very like patients with anterior infarction.

Pseudo infarction with right ventricular hypertrophy

Since right ventricular hypertrophy adds both anterior and rightward QRS forces the pseudo infarction frequently diagnosed is posterior lateral in location. The differential diagnosis between right ventricular hypertrophy and posterobasal infarction has been presented by several authors.⁵⁻¹¹ If the major QRS axis is in the left anterior quadrant of the horizontal plane

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that this may occur in subjects free of right ventricular hypertrophy or posterior myocardial infarction

Superior and inferior divisional blocks (references 2 to 16 173 to 188)

Rosenbaum's concept of the trifascicular ventricular conduction system consisting of the right bundle branch and a left branch composed of two divisions has received a wide acceptance as has his terminology for conduction disorders in the divisions of the left bundle as anterior and posterior hemiblock.¹⁷³ The characteristic electrocardiographic and vectorcardiographic alterations induced by poor conduction in the divisions of the left bundle have been reproduced by intra coronary injections¹⁷⁴⁻¹⁷⁷ and by surgical interruption in animals and in humans. Intermittent conduction disorders have been observed in some subjects.¹⁷⁷⁻¹⁸⁰ Rosenbaum's contribution to the understanding of ventricular conduction disorders is extremely important. However, two aspects of his conception and terminology probably require refinement. All the diagnostic features which will be described for fascicular blocks are derived from the frontal reference plane, owing to changes in the Y axis.¹⁸¹ Very simply stated a markedly superior shift in the frontal plane corresponds to superior divisional block or, in Rosenbaum's terminology, left anterior hemiblock. On the other hand a markedly inferior and somewhat rightward shift occurs with inferior divisional block referred to by Rosenbaum as left posterior hemiblock.¹⁷³ Since neither the anterior or posterior directions are reflected in the frontal reference plane the terms anterior and posterior to describe these changes are probably inappropriate and should be replaced by superior and inferior.

Anatomical studies in recent years have confirmed that the left bundle branch ramifies more extensively than previously thought with a third or anterior fascicle commonly present. Obviously the term hemiblock does not properly fit a trifascicular division of the left bundle branch.¹⁸² Instead of hemiblock the term divisional block seems more appropriate as it allows characterization of conduction disorders in the third or anterior fascicle and even leaves room for future anatomical discoveries.

For these reasons the portions of this review dealing with divisional blocks of the left bundle the terms superior divisional block and inferior

divisional block will be used rather than the more commonly accepted hemiblocks.

Readers are reminded that for decades myocardial infarctions on the diaphragmatic surface of the left ventricle were referred to as posterior infarcts and that many years of educational activity were necessary before the term inferior infarction was accepted. Posterior infarction has come to mean infarction of the posterobasal segment of the left ventricle and is quite distinct from inferior infarction.¹⁸³ Anterior divisional block does exist but it results appropriately in an anterior shift of QRS which may be quite distinct and separate from a superior axis shift—as discussed in a prior section. The typical vectorcardiographic changes of superior or inferior divisional block uncomplicated by other pathology, are easy to describe and to understand. Excellent descriptions and examples may be found in all of the general references given in the first section of this review.¹ In superior divisional block the major change is a shift of the major axis of the frontal plane loop to a markedly superior position lying above the X axis and commonly well above. The rotation is always counterclockwise. The initial forces in uncomplicated superior divisional block are almost invariably directed to the right and inferiorly owing to unopposed activation of the septum from the uninvolved branches of the conducting system resulting in a distinctly more inferior orientation than is usual for normal early activation.¹⁸⁴

This markedly inferior and rightward orientation of initial vectors is responsible for one of the diagnostic dilemmas occasionally encountered in uncomplicated superior divisional block.¹⁸⁵ This is the appearance of small but distinct Q waves in the right precordial leads particularly in Lead V₁ and V₂.¹⁸⁶ The Q waves result because the initial forces as described above are oriented so inferiorly as to register as negative deflections in the precordial lead axes.

The horizontal loop however exhibits its usual smooth counterclockwise course with the major vectors oriented left and posterior as in the normal case. In patients with intermittent superior divisional block slight prolongation has commonly been observed but never beyond the upper limits of normal.¹⁸⁷⁻¹⁸⁹ Terminal fluttering of time dashes is sometimes also seen. These observations indicate that the disorder is indeed a conduction delay.

Inferior divisional block produces the expected

Infarction and pseudo infarction after coronary bypass surgery

Between five and 25% of patients undergoing coronary artery bypass surgery develop new Q waves postoperatively commonly attributed to postoperative myocardial infarction. Vectorcardiographic study has been performed pre and postoperatively in such patients and a higher recognition rate for infarction has been claimed for the vectorcardiogram.^{13, 14}

However it should be pointed out that QRS voltage changes may occur as a result of alterations in postoperative hematocrit rather than true cardiac pathology.¹⁵ Further when new Q waves are correlated with bypass graft patency and postoperative ventriculograms some patients with new Q waves are found to present with patent grafts to the presumed infarcted area which exhibits normal contractility in contrast ventriculographic study.¹⁵ Thus at least some of the new Q waves seen postoperatively may be the result of something other than myocardial infarction—and should be included in the list of causes of pseudo infarction. Infrequently pseudo infarction is encountered with hyperkalemia¹⁶ or straight back syndrome.¹⁷

Right bundle branch block (references 2 to 16 161 to 172)

The experimental vectorcardiography of right bundle branch block has been studied in humans—catheter induced in the right ventricle postoperatively (after repairs of ventricular septal defects) and in patients whose conduction disorder was intermittent or was induced by premature atrial stimulation.^{18, 19}

From these observations it can be reasonably stated that right bundle branch block is essentially a distal disorder of conduction leaving unaffected the initial 40 msec of the QRS complexes. Beginning at about 60 msec after the E point the QRS loop deviates anteriorly and to the right with the terminal forces exhibiting clustered time dashes due to slower activation in the right side of the septum and the right ventricle.^{4, 6} Thus it is evident that in right bundle branch block the QRS loops are prolonged in duration (increased number of time dashes) to values of 110 to 170 msec or even longer.

The sparing of initial forces indicates that those diagnoses which depend on alterations in the earlier QRS vectors (such as myocardial infarction

and even left ventricular hypertrophy) could still be established in the presence of right bundle branch block.

Several authorities have suggested abandonment of the term right bundle branch block in favor of right ventricular conduction delay thus eliminating the unsatisfactory term incomplete right bundle branch block which has been used to describe a similar electrocardiographic and vectorcardiographic picture but with a shorter total time duration than 120 msec. In the authors' experience right ventricular conduction delays with a total duration of less than 120 msec usually exhibit the terminal slowing right and posterior to the E point while in instances with conduction prolongation to 120 msec or greater terminal delay is more commonly anterior and rightwards.

The characteristic horizontal plane QRS loop in right bundle branch block is very easy to recognize. The initial portions of the loop are very similar to the normal QRS with counterclockwise movement from the E point beginning in an anterior direction and with the major QRS forces oriented to the left and posterior. Instead of returning to the E point however the QRS loop continues and inscribes a large appendage anterior and to the right of the E point usually with counterclockwise rotation in the appendage and with clustering of the time dashes.^{16, 19}

The frontal QRS loop has a normal axis that is an orientation inferior to the X axis and to the left of the E point. The initial portion of the QRS loop may be normal in the frontal plane with either clockwise or counterclockwise rotation but the characteristic feature is the terminal appendage which is always oriented to the right but may be inferior or superior to the E point. In uncomplicated right bundle branch block the frontal axis is neither markedly superior nor markedly rightwards as is the case when a left divisional block is superimposed.^{17, 20}

The horizontal plane T loop in right bundle branch block is characteristically left and posterior with clockwise rotation. The T loops in right bundle branch block and its variations will be described in a separate section on T loops. Occasionally in the acute and experimental varieties of right bundle branch block described above the body of the QRS loop is inscribed completely anterior to the E point and may even exhibit clockwise rotation.²⁰ It is important to realize

sional block'.¹¹ However the frontal plane vectorcardiographic loop is quite characteristic and easy to recognize. The initial forces are always superior and may be oriented to the left or right. The major axis of the loop is distinctly vertical, close to the Y axis, and terminal slowing oriented to the right is always present as in uncomplicated right bundle branch block.

Various configurations of the QRS loop have been described in the horizontal plane with clockwise, counterclockwise, and figure of eight loops occurring with about equal frequency. In the series of Varriale and Kennedy¹⁰⁸ who reported 12 patients with this combination, all the horizontal plane loops, initial forces were anterior or directly leftwards. The horizontal plane loops present terminal rightward anterior conduction delay with clustering of time dashes characteristic of right bundle branch block. Many horizontal loops of patients with combined right bundle branch block and inferior divisional block have very prominent anterior QRS forces unrelated to the presence of dorsal myocardial infarction or of right ventricular hypertrophy. Thus this particular combination of divisional blocks again presents the opportunity for overdiagnosis of prominent anterior QRS forces. Five of Kennedy and Varriale's patients had well established inferior infarction in addition to their conduction disorders and in two anterior infarction was also present. Before the diagnosis of right bundle branch block combined with inferior divisional block is made, four other entities must be considered. These are right bundle branch block combined with one of the following: right ventricular hypertrophy, chronic pulmonary disease, slender body build, or extensive lateral infarction.

Ordinary clinical examination is usually sufficient to rule out the first three of these possibilities and in the last, abnormally large and prolonged early rightward forces might suggest the correct diagnosis.

Obviously, right bundle branch block combined with inferior divisional block produces a marked vertical shift in the frontal plane axis, while right bundle branch block combined with superior divisional block produces a marked superior shift in the frontal plane axis. In some patients with chronic right bundle branch block, the associated inferior or superior divisional block may be intermittent and it was from observations of axis shift in such cases that Rosenbaum¹¹² first deduced

logically the concept of a multidivisional conducting system arising from the left bundle branch.

Myocardial infarction combined with superior or inferior divisional block (references 2 to 16, 199 to 209)

Inferior myocardial infarction combined with superior divisional block results in a characteristic and easy to recognize frontal vectorcardiographic loop.¹⁰⁹⁻¹¹¹ The initial 25 to 40 msec of the loop reflect the inferior infarction.

The generated QRS forces are superior to the E point and rotate to the left along the X axis within the 25 and usually the 30 msec vector superior to the X axis.¹¹² The loop then turns superiorly and changes its rotation from clockwise to counterclockwise so that the bulk of the QRS loop lies superior to the X axis.¹¹³⁻¹¹⁵ Thus, while the initial forces reflect the inferior infarction, the terminal forces reflect the superior divisional block. A frequent electrocardiographic problem is the interpretation of records displaying QS or QR complexes in leads 2, 3, and aV_F. When a frontal loop as just described is present, combined inferior infarction and superior divisional block is evident.¹⁰⁹ However, if the frontal loop is markedly superior but exhibits clockwise rotation throughout the diagnosis is inferior infarction, probably extensive but without combined superior divisional block.¹¹⁶ As Benchimol¹¹⁷ has pointed out, the combined diagnosis is of great predictive value in assessing possible coronary artery obstruction, since inferior infarctions are generally associated with right coronary artery lesions, while the superior division of the left bundle is nourished by the left anterior descending artery.¹¹⁸ Thus, when the combined diagnosis is made, double coronary vessel disease should be suspected clinically.

In other patients with inferior infarction the axis is markedly vertical or even rightward, despite the initial prolongation of superior forces characteristic of inferior infarction.¹¹⁹⁻¹²¹ Here the diagnosis is inferior infarction combined with inferior divisional block. This is a combination probably described previously by First and associates¹²² as inferior infarction with "pen infarction block." In some patients with inferior myocardial infarction, injection of contrast material into the right and left coronary arteries successively produces an associated inferior and

opposite picture in the frontal plane¹⁰. The initial forces are oriented superiorly and usually to the left and the major QRS vectors are always directed inferiorly and usually to the right¹¹⁻¹⁴. The loop rotation in the frontal plane is practically always clockwise. The late rightward forces observed in the frontal plane of course are also apparent in the horizontal plane which maintains its normal counterclockwise rotation with initial forces inscribed anterior and to the left. It is apparent from this description that the QRS loops in the horizontal and frontal plane of inferior divisional block closely resemble the description of loops in Type C right ventricular hypertrophy as commonly observed in mitral stenosis, emphysema and cor pulmonale.

Superiorly displaced frontal loops resembling those of superior divisional block may also occur with emphysema. Hyperkalemia may occasionally present with a marked superior or inferior frontal axis which may indeed represent superior or inferior divisional block respectively as these changes are reversible with correction of the electrolyte abnormality¹⁵. A special type of counterclockwise superior frontal loop is commonly seen in patients with endocardial cushion defects¹⁶. In these cases the anatomic length of the superior division is prolonged as it courses along the anterior surface of the defect while the inferior division is much shorter. This discrepancy in length results in sequential rather than simultaneous activation of the myocardium supplied by the superior and inferior divisions respectively with a resultant superior counterclockwise frontal loop resembling in every way superior divisional block.

Right bundle branch block combined with superior divisional block (references 2 to 16 189 to 196)

When right bundle branch block is combined with superior divisional block the terminal conduction delay oriented to the right and anterior with clustered time dashes is unchanged¹⁷. However a marked superior shift in the frontal plane axis occurs with the body of the QRS loop prior to the terminal appendage being inscribed well above the X axis and with counterclockwise rotation—as in the case of uncomplicated superior divisional block. The initial QRS forces are practically always inferior in location and may be inscribed either to the right or to the left¹⁸.

In the transverse or horizontal plane two

morphologies designated types A and B by Lichstein and associates¹⁹ have been described and confirmed by several other observers.

In the more common type A horizontal loop the body of the loop is inscribed counterclockwise and to the left with the maximum vector either anterior or posterior. The terminal appendage then follows characteristically oriented to the right and anterior of the E point. In the type B horizontal loop the sense of rotation is clockwise with the entire QRS loop oriented to the E point.

In several clinical investigations attempts have been made to correlate these type B loops with associated dorsal myocardial infarction or right ventricular hypertrophy but without significant success as the majority of such cases lack other stigmata of these conditions. However the type B loops are associated with a somewhat higher incidence of proven organic heart disease, ventricular hypertrophy, etc.²⁰

In the author's view the type B loops probably represent additional delay in the anterior or midseptal fascicle of the left bundle branch system. Delay in that branch would account for anterior displacement of the QRS loop and for the clockwise rotation observed without invoking additional hypertrophy or infarction. In this type B loop of right bundle branch block combined with superior divisional block the vectorcardiographer encounters yet another circumstance in which overdiagnosis of prominent anterior forces in this instance combined with clockwise rotation may easily lead to mistaken diagnoses of serious organic heart diseases. At least partial confirmation of the concept of anterior conduction delay in the genesis of the type B loop is found in the work of Cohn and colleagues²¹ who demonstrated a variety of ventricular aberrations following stimulated atrial premature beats some of which exhibited vectorcardiographic loops identical to the type B loop described above in the absence of dorsal infarction or right ventricular hypertrophy and which were intermittent. At slower heart rates the vectorcardiographic loops in these individuals were perfectly normal.

Right bundle branch block combined with inferior divisional block (references 197-198)

The combination of complete right bundle branch block with inferior divisional block is considerably less frequent than the combination of right bundle branch block with superior divi-

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then superior divisional block on a temporary basis. The combination of inferior infarction with inferior divisional block produced by such experiments is quite similar to loops described as inferior infarction with per infarction block.

In contrast to the above anterolateral infarction accompanied by superior divisional block would result in a frontal plane loop characterized by abnormally prolonged and large initial rightward forces (lateral infarction) followed by a continuation of the loop superiorly and counter clockwise in the left superior quadrant of the frontal plane—with these terminal forces characteristic of superior divisional block. Thus the criteria for so called per infarction block would be met with the initial vectors opposite the terminal vectors. Experimentally patients with anterolateral infarction may have a picture closely resembling per infarction block superimposed by selective injection of the left coronary artery.

Although the author believes that most cases described as per infarction block probably represent infarction combined with a divisional block, it still remains possible that in some instances the conduction disturbance is indeed peripheral and is localized in the ischemic tissue around the necrotic zone of the infarction.¹⁰

Since the diagnoses of superior or inferior divisional block are made from the frontal plane vectorcardiogram which does not display anterior/posterior forces, the diagnosis of associated anterior infarction rests with the disposition of the initial vectors in the horizontal reference plane.

Thus characteristic deformities as described in the section on anterior infarction will co-exist with typical terminal frontal loop abnormalities characteristic of either superior or inferior divisional block as described above. One special variety of infarction combined with divisional block deserves particular mention. This is true dorsal infarction combined with inferior divisional block. Here in the transverse plane the initial half of the loop is displaced anteriorly to the left anterior quadrant of the horizontal plane while the major axis in the frontal plane is oriented inferiorly with clockwise rotation. This vectorcardiographic QRS loop obviously closely resembles Type B or Type C right ventricular hypertrophy but in fact may on occasion really represent a combination of inferior divisional block with an

terior conduction delay. The reader is reminded that anatomical studies reveal that the anterior fascicle of the left bundle branch frequently arises from the inferior division. Thus fibrosis or scarring of that division proximal to the bifurcation into the inferior and midseptal divisions could well account for this last vectorcardiographic picture described.

The entire subject of myocardial infarction complicated by intraventricular conduction disturbances is beautifully outlined in program form by Lemberg and Castellanos in their book, *Vectorcardiography*.

In that text and in at least one publication¹⁰ Castellanos advances the concept of intra infarction block. This diagnosis is to be suspected when the Q waves produced by an infarction or the corresponding portion of the vectorcardiographic loop exhibit slurring or notching lasting 20 msec. The genesis of this abnormality may well be islands of living myocardium within the infarcted zone. These islands by contributing relatively normal QRS voltages during the subtraction effect of the infarcted tissue surrounding result in an interruption of the usually smooth initial defect resulting from the infarction.¹⁰ This is an interesting and valuable conception and may well explain the observed phenomenon which is encountered occasionally in vectorcardiographic tracings.

Right bundle branch block combined with myocardial infarction (references 2 to 16, 199 to 209)

When right bundle branch block is combined with inferior wall infarction the diagnosis is quite easy by vectorcardiogram. The reason is simple enough. The right bundle branch block, which displaces the terminal QRS forces right and anteriorly as previously described, is not only a distal phenomenon in the QRS loop but is most evident in the horizontal reference plane. Although the terminal rightward delay is evident in the frontal plane the initial 25 to 40 msec of the QRS loop are not affected and still will reveal the characteristic abnormality of myocardial infarction of the inferior wall.

Lateral myocardial infarction which is generally diagnosed on the basis of a prolongation of initial rightward forces beyond the normal value of approximately 25 msec is likewise evident in both the horizontal and frontal references even

cardiogram exhibiting left bundle branch block, accurate localization is possible in about half the cases although many remaining patients do indeed have infarctions but in unexpected areas Goldman and Pipberger¹¹ have identified other criteria useful in recognizing infarction in the presence of left bundle branch block. An absence of an anterior ST junctional displacement was indicative of infarction at the 95th percentile level and a T magnitude in the horizontal plane of less than 0.2 millivolts was also indicative of infarction at the 95th percentile level. Goldman and Pipberger¹¹ also confirmed the importance of initial rightward QRS forces or prominent anterior forces as criteria for myocardial infarction in the presence of left bundle branch block. In the series of Goldman and Pipberger the total identification rate was 50% with 14% false positives. These results were approximately equal to the diagnostic power of the vectorcardiogram in identifying myocardial infarction in the presence of right bundle branch block. These autopsy confirmed VCG patterns for myocardial infarction in the presence of left bundle branch block resemble very closely the vectorcardiograms produced by Bistoni and colleagues²⁷ who used phenol injections to induce areas of necrosis in experimental animals with previously induced left bundle branch block. The above data are rather convincing in establishing the value of vectorcardiography in the assessment of patients presenting with left bundle branch block and in whom coronary artery disease with infarction or myocardial fibrosis is suspected clinically.

Incomplete left bundle branch block

In so called incomplete left bundle branch block the total duration of the QRS loops is between 100 and 120 msec. In general these loops resemble those of left bundle branch block except that the duration is shorter. In the characteristic case the initial forces are oriented to the left and anterior in the horizontal plane which may retain its usual counterclockwise rotation but occasionally is figure of eight with the proximal section counterclockwise and the distal section clockwise.

The frontal loop is oriented close to the Y axis but not above it with characteristic counterclockwise rotation. Scalar electrocardiographic features of left ventricular hypertrophy are often present in these cases.

Right ventricular hypertrophy with left bundle branch block (reference 223)

A little known application of the vectorcardiogram in left bundle branch block is the diagnosis of right ventricular hypertrophy. Chou and Helm²²³ described five patients with unequivocal right ventricular hypertrophy whose vectorcardiograms could easily be recognized as typical of left bundle branch block. The contour of the horizontal loops, the mid and terminal slowing and the clockwise rotation were all characteristic. The QRS loops were prolonged and the initial QRS forces were oriented to the left and inferiorly. However in two ways these loops differ from the typical uncomplicated stereotype of left bundle branch block. These were the rightward displacement of the body of the QRS loop and the leftward orientation of the ST vector and T loop.

Although as described above rightward displacement of QRS may be seen in left bundle branch block complicated by myocardial infarction there are distinct differences from Chou and Helm's patients²²³ with right ventricular hypertrophy. When marked rightward deviation is present secondary to infarction in left bundle branch block the displacement is initial or terminal with the bulk of the loop still oriented to the left and posteriorly. Further when early forces are displaced to the right in myocardial infarction complicated by left bundle branch block the rotation is generally rightward and clockwise about the E point whereas in left bundle branch block complicated by right ventricular hypertrophy the early rotation about the E point is counterclockwise. The cardiologist is encouraged to become familiar with the normal stereotype of left bundle branch block and with the variations described from which myocardial infarction or right ventricular hypertrophy may be suspected. In the author's opinion patients with left bundle branch block present frequent opportunities for additional diagnosis from the vectorcardiogram and the test should be employed frequently in these individuals.

Right bundle branch block combined with right ventricular hypertrophy (references 2 to 16, 224 to 228)

Baydar and colleagues² presented a classification of right bundle branch block in relation to right ventricular hypertrophy and chronic pulmo-

diagnosis beyond the conduction disorder is ble. However a surprising amount of information is available from careful examination of loops in left bundle branch.

¹ Indeed Goldman and Pipberger have demonstrated that vectorcardiographic criteria are about as accurate in identifying the presence of myocardial infarction accompanying left bundle branch block as in the case of right bundle branch block.

In order to use the vectorcardiogram properly in left bundle branch block the cardiologist must become familiar with the stereotype of left bundle branch block as it is encountered in the absence of cardiac abnormality or as produced experimentally.

¹ Under such circumstances a rather typical picture is seen. The initial QRS forces are oriented to the left and anteriorly and always rotate in a counterclockwise manner with a duration of anterior forces about 10 to 20 msec. ¹ The second vectorial movement as outlined by Scott ¹² is directed leftward posteriorly and inferiorly attributed by Bisteni and colleagues ¹ and also by Wallace and associates ¹ to right to left activation of the interventricular septum. At about 50 msec the third vector appears. This is directed leftward superior and posterior and exhibits slurring and clustering of time dashes. Here the rotation changes from counterclockwise to clockwise and this sense of rotation persists for the duration of the QRS loop as seen in the horizontal plane. The last vector the fourth which corresponds to the returning limb or the afferent portion of the QRS loop is oriented posterior and left and is attributed to activation of the left ventricular free wall. The closest spacing of time dashes is during the inscription of the third vector described above.

In the frontal reference plane the initial forces are oriented to the left and inferiorly. The loop is inscribed in a counterclockwise manner usually inferior to the λ axis although the terminal forces may be inscribed above the λ axis. The T loop in the horizontal plane is oriented to the right and anterior and is usually counterclockwise while in the frontal plane it is right and inferior and also counterclockwise. ¹³ Neuman and colleagues and Pietras and co-workers have evaluated various criteria for myocardial infarction in patients with left bundle branch block followed to necropsy and subjected to detailed postmortem examination of the heart. In all six variations

from the typical stereotype of left bundle branch block were considered and evaluated as infarction criteria. Clockwise rotation of the initial forces of the QRS loop about the E point in the horizontal plane was evaluated as a criterion for septal infarction. Of 13 such patients all had myocardial infarction or fibrotic areas six of which were concentrated in the ventricular septum. The remaining patients had infarction or fibrosis in other myocardial areas. A posterior position of the 01 sec vector as seen in the horizontal plane was tested as a criterion for anterior apical infarction. Of nine such patients four had infarction or fibrosis of the anterior wall and the remaining five had fibrosis or infarction but located in other areas.

Rightward displacement of the afferent limb (but not crossing to the right of the E point) was evaluated as a criterion for lateral infarction. Six patients presented such vectorcardiograms and five had either infarction or fibrosis of the lateral wall. The remaining patient had a septal infarct.

Displacement of the afferent limb of the QRS to a point greater than 0.05 millivolts to the right of the E point was evaluated as a criterion of anterolateral infarction. Of 14 patients with this abnormality seven had infarction or fibrosis in the anterior and lateral areas six patients had infarction or fibrosis in other areas and one patient had left ventricular hypertrophy. An anterior position of the 02 sec vector was evaluated as a criterion for true posterior infarction. Seven patients met this criterion of whom five indeed had posterior infarctions at necropsy. The remaining patients had infarction or fibrosis in other areas. A superior frontal mean axis (between -30 and -180 degrees) was evaluated as a criterion for myocardial infarction. Of 21 patients with such a superior axis 14 had infarctions demonstrated at autopsy. In the largest group (ten patients) the infarction was dorsal in location. All the remaining patients had infarction or fibrosis in other areas and several had ventricular hypertrophy as well. In comparing the performance of vectorcardiographic versus electrocardiographic diagnosis it was very evident that the vectorcardiogram was quite superior in the diagnosis of infarction in the present of left bundle branch block. ¹⁴ However the authors of these studies point out that when criteria for infarction are met by a vector

ular system an initial delay is noted in the QRS loop which is directed away from the point of origin of the ectopic beat. In this respect, such loops are similar to those generated by pacemaker stimuli or via AV bypass tracts in the pre-excitation syndromes.³¹

After the initial delay, which varies in duration from 20 to 40 msec, rapid conduction may follow usually oriented in the same direction as the initial forces. This probably represents entrance of the activation wave into an adjacent fascicle. A change in direction then commonly occurs as myocardium not activated by the initial fascicle depolarizes and this in turn is followed by slow activation of the ventricle opposite the site of initial ectopy. When the ventricular point of origin of the premature beat is not near a segment of the fascicular system the initial delay may not be followed by as many directional changes until activation of the opposite ventricle occurs.³²

Probably the most important feature of vectorcardiography in ectopic ventricular beats is the detection of the initial slowing which serves to locate the point of origin of the ectopic beat.³³ As has been pointed out by several authors, inspection of the scalar ECG or even of orthogonal leads may not be sufficient in localizing this initial delay which may be apparent only as a step in the VCG loop.^{34, 35}

Talbot and associates³⁶ have located the initial forces in ventricular ectopic vectorcardiograms using the 360 degree planar reference system for the frontal and horizontal planes. It is evident from their data that these initial slow forces may be located anywhere, indicating a large variety of possible ventricular sites of origin in either ventricle. The majority of initial delays were located to the left of the E point in the frontal plane, mostly inferior and either anterior or posterior to the E point when considered in the horizontal plane. The rotational characteristics of the QRS loops resulting from ventricular ectopy were highly variable. Clockwise rotation in the horizontal plane was a common finding.

The QRS loops resulting from pacemaker stimulation are similar in many ways to the vectorcardiographic loops arising from spontaneous ventricular ectopy. The entire QRS loop is prolonged in duration owing to conduction delay in the ventricle opposite the one stimulated. Thus with right ventricular stimulation the major axis of the induced QRS loop is leftward and the oppo-

site situation prevails with left ventricular stimulation.^{37, 38} Pacemaker stimulation inferior in a ventricle will result in a superiorly directed QRS loop while electrodes placed in the outflow tract will result in inferiorly placed loops. Similar considerations apply to anterior and posterior direction—with anterior positioning resulting in posterior loops. Castellanos and co-workers³⁹ have succeeded in reproducing spontaneously occurring VPC configuration by selective stimulation of various portions of the right ventricle or left ventricle by placement of the pacing electrode at the right ventricular apex in the coronary sinus or within the middle cardiac vein.

An invariable feature of pacemaker vectorcardiographic loops is an initial delay entirely similar to that seen frequently in ventricular ectopy.⁴⁰ This initial delay in most frequently oriented inferior and left, about half are anterior and half are posterior.⁴¹ The body of the QRS loop may be clockwise, counterclockwise, or figure of eight in all three reference planes with the commonest finding a figure of eight loop in both horizontal and frontal planes.^{42, 43, 44} Since infarction induces changes in the vectorcardiographic loops of left bundle branch block (which right ventricular paced loops resemble), attention has been paid to similar changes in the pacemaker VCG loops of patients with underlying myocardial infarction.^{45, 46, 47} Not surprisingly, the induced QRS loops are indeed modified and resemble very closely the variations produced in spontaneous left bundle branch block by myocardial infarction as occurring under natural or experimentally induced conditions.⁴⁸ With inferior myocardial infarction the right ventricular paced vectorcardiographic loop is oriented superiorly with initial delay, also oriented superiorly and with clockwise rotation of the frontal plane loop.^{49, 50} In true posterior infarction the initial delay was oriented markedly left and anterior with counterclockwise rotation of the induced horizontal loop. This picture according to Zonerach and Zonerach⁵¹ is unique. With infarction of the anteroapical areas the initial QRS vectors were oriented right and posterior with clockwise rotation of the horizontal plane loop—thus closely resembling the alterations produced in naturally occurring left bundle branch block complicated by anteroapical infarction.⁵² The stimulus artifacts from unipolar catheters are about ten times larger than those produced with bipolar

ary disease based upon the horizontal plane on of the afferent (returning) limb of the QRS loop. Thus in patients with an afferent limb r to the E point no right ventricular hypertrophy or pulmonary disease was expected. In a second group the afferent limb was anterior the E point but the loop rotation remained clockwise. Here an increased incidence of ventricular hypertrophy and chronic pulmonary disease was encountered. In the third group only was the afferent limb anterior to the E point but the entire loop exhibited a clockwise rotation. Here the incidence of right ventricular hypertrophy or chronic pulmonary disease was the highest.

In a recent reevaluation of these criteria Fedor and colleagues²² confirmed an increasing incidence of cardiac failure or severe pulmonary disease as vectorcardiograms were arranged according to these three groups designated as Types I, II and III. Although Fedor and associates concluded that the Type III variety was a reliable guide to cardiac failure or severe pulmonary disease—and indeed even to pulmonary hypertension—their data indicate that five of 31 patients falling into this Type III group (16%) had only insignificant cardiac or pulmonary disease. The reader is here referred to prior discussion of right bundle branch blocks combined with divisional block induced by atrial premature stimulation. This commonly results in transient aberration and vectorcardiographic loops identical with the Type III variety as commonly encountered clinically and associated with chronic pulmonary disease.

Chou and associates²³ studied children with right ventricular hypertrophy determined at cardiac catheterization who had both pre and post operative vectorcardiograms with the latter exhibiting a new right bundle branch block. These patients without question reflected in their second vectorcardiogram the combination of right and left bundle branch block associated with right ventricular hypertrophy. Chou and colleagues were unable to confirm that clockwise rotation in the horizontal plane was a reliable indicator for such right ventricular hypertrophy as the sense of rotation changed in 50% of the operative patients who developed postoperative right bundle branch block. However these authors did offer three criteria which were useful in children.²³ These were a maximum QRS vector directed to the right

of 65 degrees in either the horizontal or frontal plane a maximum rightward vector exceeding the normal value for age (generally a value greater than 10 millivolts) and lastly an abnormal ratio of leftward to rightward QRS forces (RY/SX) the critical value being 0.91 in the oldest age group studied (ages 10 to 16 years).

The T loops in right ventricular hypertrophy with or without bundle branch block are oriented to the left with clockwise rotation in the horizontal plane and are usually located posterior to the E point.²⁴ Additional discussion of the T loops in right bundle branch block and in RVH is to be found in a subsequent section devoted entirely to T loops. Clearly the vectorcardiographer attempting the diagnosis of RVH in the presence of a right bundle branch block on the basis of a prominently anterior and clockwise horizontal loop is liable to make mistakes. A very similar picture as described above has been found with right bundle branch block combined with superior divisional block or combined with true dorsal infarction. Conduction delay in the anterior fascicle may also play a role especially when another divisional block is already present. However when even a modicum of clinical information is available the vectorcardiographic diagnosis may be pronounced with more authority.

The vectorcardiography of premature ventricular or pacemaker induced complexes (references 229 to 242)

Despite the technical difficulty in obtaining vectorcardiograms of ventricular premature contractions several authors have accumulated a sizable series of such beats.^{10, 21, 25} Although several varieties of loop disturbances have been described they are readily understandable in the light of published information on the vectorcardiography of bundle branch and fascicular blocks.

For example about twenty % of ventricular premature beats exhibit vectorcardiograms which are indistinguishable from uncomplicated right or left bundle branch block.²⁶ It may be presumed that the beats resembling right bundle branch block arise in the left main bundle branch while those resembling left bundle branch block arise in the right main bundle.^{2, 27} The large majority of ventricular ectopic beats however are considerably more complex but nevertheless understandable. When the ectopic focus is outside the fascic

direction or rotation abnormal width in addition is of little value in diagnosis as all presently described T loop abnormalities be they secondary to conduction delays hypertrophy or ischemia have the capacity to widen the T loop

Scalar electrocardiographers have long been used to the term primary or secondary T wave abnormalities and a parallel exists in vectorcardiography The secondary T loop abnormalities may be attributed to alterations in the repolarization sequence as seen in right or left ventricular hypertrophy and right or left ventricular conduction disorders^{219 221 222 223 224} Primary repolarization abnormalities are attributed to local disorders of recovery, usually in segmental ischemic zones of the left or right ventricles

The basic change in recovery physiology in an ischemic zone is a prolongation of action potential Thus the last portion of the myocardium to generate recovery potentials is the ischemic zone and owing to the return of the unaffected myocardium to resting potential by that time the observed T wave and T loop must be directed away from the area of ischemia Smith and colleagues¹⁷ noted marked shifts in the direction of the T loops during right or left coronary artery injection respectively with contrast material Right coronary artery injection producing transient ischemia of the inferior wall resulted in a leftward and superior shift of the T loop resembling the direction observed in clinical inferior infarction with a surrounding ischemic zone In contrast left coronary injections caused a shift of the T loop to the right and inferior entirely similar to changes observed with lateral myocardial ischemia These changes were of course transient and reversible

Several authors have described the T loop abnormalities seen in coronary artery and other myocardial diseases^{1 6} In general ischemic T loops change in direction as noted above with their long axis directed away from the ischemic zone

In addition the length/width ratio changes so that the loops are characteristically oval with the most terminal portions of the T loop opposite the area of slow repolarization Thus a rather circular loop in which the early basal forces may be anterior with the terminal forces posterior is commonly seen with anterior myocardial ischemia This type of loop results in a plus minus T wave in the precordial leads

Similar considerations ap

ply to inferior, lateral and dorsal ischemia In this latter condition since the T loop is normally anterior and left the development of dorsal ischemia may shift the T to a directly anterior position However because of lateral ischemia which is often associated the most terminal T forces are oriented the most medially resulting in a change in rotation of the horizontal T loop from counterclockwise to clockwise In a T loop of normal width clockwise rotation in the left anterior quadrant is almost never seen in normals²²⁵ In the presence of clinically suspected coronary disease such a vectorcardiographic observation should be taken as evidence favoring dorso lateral ischemia Vectorcardiographic T loops exhibit another interesting characteristic in many cases The terminal T forces may exhibit slowing so that the entire loop is evenly inscribed, corresponding to the symmetrical T wave commonly encountered in scalar electrocardiography and recognized as characteristic of myocardial ischemia^{226 227}

An excellent programmed introduction to the vectorcardiography of T loops was presented by Castellanos and colleagues²²⁸ It should be emphasized at this point that the vectorcardiographer interpreting an ischemic T loop is really considering three repolarization phenomena all simultaneous with the observed T loop the resultant In a case with a localized area of left ventricular ischemia the balance of the left ventricle may well be generating perfectly normal T potentials and a normal T loop The right ventricle may similarly be generating a normal right ventricular T loop Thus the observed T loop represents the summation of the normal left and right ventricular repolarization with the ischemic repolarization added

The secondary T loop abnormalities observed in left ventricular hypertrophy and the left ventricular conduction delays (left bundle branch block right ventricular pacing and ventricular premature beats arising in the right ventricle) are all very similar²²⁹ Since these conditions are the pure form do not affect the right ventricle the T loop generated by the right ventricle is in its usual position—anterior However the hypertrophy or conduction disorder affecting the left ventricle alters the recovery sequence so that the resulting T loop is directed opposite the observed QRS and becomes located to the right and anterior of the E point The right anterior T loop

tumulation owing to the much greater distance between the negative electrode and the pulse generator in the case of a unipolar pacemakers compared to the approximately ten mm distance between negative and positive poles with bipolar catheters.¹ Therefore the stimulus artifact with unipolar pacemakers is directed from the catheter to the anatomic location of the battery pack, whereas with transvenous bipolar catheters placed at the apex of the right ventricle the vector representing the stimulus artifact is usually directed to the right and superior. Much greater variation is possible in the case of left ventricular catheters which may be placed anywhere on the ventricular surface. A change in axis of the stimulus artifact from a bipolar pacing catheter may result from wire breakage as the stimulation changes from bipolar to unipolar with the artifact axis now depending upon the location of the battery pack and the site of ventricular contact proximal to the break.

Pacemaker vectorcardiography and the vectorcardiography of ectopic ventricular beats have provided a fascinating confirmation of the information so laboriously accumulated concerning bundle branch blocks, fascicular blocks, the pre-excitation syndrome and their combinations with myocardial infarction.

Zoneraich and colleagues² have correlated the electrocardiographic and vectorcardiographic findings resulting from right ventricular pacing with echocardiography of the intraventricular septum. A posterior twitch of the left side of the septum entirely similar to that described in spontaneous left bundle branch block has been observed with pacemaker stimulation—except that this twitch occurs about 30 msec later (probably owing to the initial delay occurring with pacemaker excitation of the heart). No doubt future studies will extend these observations in which echocardiography and vectorcardiography are correlated.

Vectorcardiography of the T loops (references 2 to 16, 108, 243 to 269)

Just as the QRS loops at any moment in time represent the sum of all electrical activity of the entire heart (right and left ventricles) so does the T loop represent the summation of recovery potentials in both ventricles simultaneously.² That the right ventricle contributes to the T loop

should be no surprise to any cardiologist familiar with the obvious T abnormalities seen in conditions such as right bundle branch block and right ventricular hypertrophy. Obviously, the right ventricle is capable of generating very large recovery potentials which may indeed dominate the observed T loop.

Similarly in the normal, the observed T loop is the resultant of a leftwards T loop generated by the left ventricle added to a directly anterior T loop generated by the right ventricle.^{2, 4, 11} It is the sum of these two separate repolarization phenomena that results in the normally observed T loop directed to the left inferiorly and anteriorly—thus making a rather wide angle in the horizontal plane with the left and posterior QRS loop.

The electrophysiology of repolarization has been presented by several authors^{4, 11} as has the morphology of the normal vectorcardiographic T loop.^{2, 4} In addition to the directional characteristics mentioned above, the normal T loop rotates in a counterclockwise manner in the horizontal plane and is either narrow or clockwise in the frontal plane. Some normal T loops are so elongated and slender that rotational description has little meaning. Indeed, some authors recommend that no description of rotation be made when the length with ratio of a T loop in any plane exceeds 10 to 1. Ordinarily the early portions of the T loop are written more slowly than the terminal portion accounting for the asymmetric T wave seen in surface scalar recordings.^{2, 4, 11} Thus several characteristics of the normal may be altered by changed physiology or disease states—that is the direction, sense of rotation, the length/width ratio and the speed of inscription.

Chou and associates¹² have emphasized the spatial length/width ratio in the normal and determined an upper limit of 1.6. This is calculated by dividing the maximum length in any plane by the maximum width in any plane. Occasionally the only abnormality found in a vectorcardiographic record may be an alteration in the length/width ratio such that the loop becomes ovoid with a ratio less than 1.6. In the absence of drugs such as digitalis which may cause a similar alteration, such a reduction in the length/width ratio should call attention to the possibility of organic heart disease. When other T loop abnormalities are present such as abnormal

the T loop persists but the sense of rotation changes from counterclockwise to clockwise in the horizontal plane and the T loop shifts to a posterior leftward position again with an open QRS loop. Isaacs and colleagues^{2,3} recommend simultaneous recording of the Frank XYZ leads as a useful monitoring technique in exercise stress testing. Although they recorded the vectorcardiographic loops simultaneously with exercise the use of magnetic tape recordings would permit a later generation of loops and the use of signal averaging as well.⁴ Rautaharju and co-workers⁵ have subjected P, ST, and T voltages obtained using the Frank lead system during exercise to computer analysis. Bizarro and associates⁶ recently reported the correlations of various vectorcardiographic criteria with myocardial scarring determined at autopsy. Surprisingly the most sensitive criteria found related to T wave voltage in the X, Y, and Z axes. It seems possible therefore that the entire question of specificity of vectorcardiographic T loop criteria should be reexplored.

Vectorcardiography of the P loop (references 2 to 16, 269 to 289)

The technical problems that complicate P loop study arise from the small amplitude of the voltages generated by atrial depolarization necessitating extremely high gain for proper amplification. Standardization of one millivolt equal to 20 or 40 cm have been commonly used and even higher sensitivities are possible. Several different techniques have been used in order to eliminate overlapping portions of the T or QRS loops. These techniques include gating in which only the desired portion of the cardiac cycle in this case the P wave is recorded, recording on tape followed by averaging by computer and then followed by gating, or the technique of examining running or timed loops in which the oscilloscopic beam moves from left to right while the loops are being inscribed. Using these technologies as well as simple high quality still loop vectorcardiography, a good deal of information has been accumulated about the vectorcardiography of the P complex.

Two distinct components of the P loops may be observed which in the normal person are distinctly different in magnitude and direction. The initial right atrial component is directed to the left and anterior while the left atrial component occurs later and is directed left and posteri-

orly.^{2,3,4,6} When the Frank electrode system is used the maximum P vector in the frontal plane is oriented between +30 and +90 degrees (inferior and left) while the maximum vector in the horizontal plane is oriented between -45 and -20 degrees (left and posterior). The magnitude of the maximum horizontal vector of the P loop is less than 0.12 millivolts. Criteria have been proposed by several workers for the identification of right or left atrial overload. The term overload seems preferable at this time to either hypertrophy or dilatation as changes in intra-atrial pressure or size may result in identical P loop abnormalities as observed in true hypertrophy (increased atrial wall thickness).^{2,3} Indeed the term overload may itself be too restrictive as intra-atrial conduction disorders which will also be discussed may produce P loops closely resembling those observed in left atrial overload. In right atrial overload the horizontal P loop shifts to a distinctly left anterior position and to a more vertical position in the frontal reference plane.^{2,3,4} However the duration of the P loop does not increase and therefore remains less than 100 msec in all reference planes. The maximum vector in the horizontal plane may be found between +6 and +90 degrees (the left anterior quadrant of the horizontal plane) and in the frontal plane between +50 and +120 degrees (inferior and often rightwards). The magnitude of the maximum anterior deflection exceeds 0.1 millivolts and the ratio of posterior to anterior P loop forces is usually less than one average 0.6 in the experience of Benchimol and associates.⁶ The P loop rotation in right atrial overload is characteristically counterclockwise in both the frontal and horizontal reference planes. The magnitude of the major P vector in the frontal plane is increased and equals or exceeds 0.2 millivolts.

Left atrial overload. In general although the magnitude of the major anterior P vector remains unchanged from normal (mean value 0.04 millivolts) the magnitude of the posterior P vector distinctly increases exceeding the normal mean value of 0.12 millivolts.^{2,3} Further the ratio of posterior to anterior P voltage increases and exceeds 2. The maximum horizontal vector is located between -10 and -90 degrees (left and posterior) while the maximum P frontal vector is located between +60 and -10 degrees (distinctly less inferior than patients with right atrial overload). A figure of eight rotation is common in the

secondary to the left ventricular disorders is characteristically counterclockwise in the horizontal reference plane.¹⁰⁶ Controversy exists about the diagnostic significance of a large horizontal T loop located in the right anterior quadrant of the horizontal plane in the presence of left ventricular hypertrophy or a left ventricular conduction delay.¹⁰⁶ Although originally believed to represent coronary artery disease in addition to the secondary T loop abnormality, sufficient evidence has been presented¹⁰⁷ by arteriography of such patients to indicate that uncomplicated left ventricular hypertrophy especially with a rather rightward horizontal T loop may result in a clockwise rotation of the T in the absence of significant coronary obstruction.¹⁰⁸ However in the presence of left bundle branch block such rotation probably does indicate that in addition to the secondary T loop abnormality attributable to the conduction disorder an additional ischemic zone exists.¹⁰⁹ In that circumstance three simultaneous T phenomena could again be responsible—that is, the normal right ventricular T, the secondary left ventricular T, and an ischemic left ventricular T.

Somewhat similar but occasionally more complicated considerations apply to the secondary changes in the T loop generated by the right ventricle.¹¹⁰ Here in the presence of severe right ventricular hypertrophy or right ventricular conduction delays (right bundle branch block, left ventricular pacing, or ectopic beats arising from the left ventricle) the sequence of recovery is altered in the right ventricle such that the observed T loop is located in the left posterior quadrant of the horizontal plane and typically with clockwise rotation. As might be expected from this comment there is no observable difference between the T loop in right ventricular hypertrophy and the T loop in right bundle branch block.

Rubler and associates¹¹¹ did note that in right bundle branch block complicating clinically established right ventricular hypertrophy the T loop tended to be more posterior than in uncomplicated right bundle branch block. The rotation however remains clockwise most commonly and the length/width ratio is often abnormal in both conditions.

Obviously if the vectorcardiographer confronts a QRS loop characteristic of right bundle branch block but with a T loop oriented to the right and

anterior or posterior a left ventricular abnormality complicating the right bundle branch block must be considered. Associated severe left ventricular hypertrophy could be responsible or an ischemic zone in the left ventricle.

Uniformity of inscription of such a T loop as well as its location helps to identify ischemia as the cause of the unexpected location of the T loop.¹¹²

The T loop abnormalities which accompany divisional block have not been well worked out. In many cases the T loops remain entirely normal. However in some examples observed personally or published in atlases with superior divisional block the T loop has all the characteristics of the secondary T loop abnormality observed with left ventricular hypertrophy or left bundle branch block.

In some cases of anterior conduction delay the T loops are perfectly normal while in others they assume a posterior position.

Just as myocardial ischemia in a single zone may alter the direction, shape, and rotation of a T loop already influenced by hypertrophy or conduction delay, several coexisting ischemic zones may modify one another. Thus inferior ischemia combined with lateral ischemia characteristically displaces the T loop right and superior. The sense of rotation varies with the terminal T forces directed away from the most ischemic area.

T loops should be recorded at moderate high amplification and with gating circuits when possible to remove overlapping segments of QRS and T. A useful technique is to alter the interval between time dashes during the T loop recording so that 10 msec separates each dash rather than 2 or 2.5 msec. This results in a more readily appreciated sense of rotation.

T loop abnormalities after exercise have been reported¹¹³⁻¹¹⁵ and correspond quite closely to the ST-T abnormalities found in abnormal stress testing. Isaacs and colleagues¹¹⁶ have correlated three different T loop patterns with the three characteristic ST responses to exercise: ST junctional depression with an upsloping ST segment has been correlated with an elongated horizontal T loop which remains open at its termination. When the ST segment is depressed and isoelectric a wide ovoid horseshoe shape T loop is seen again with an open QRS loop. In the most severely abnormal response, downsloping ST segment depression, the horseshoe shape of

tion delay and the vectorial orientation of these initial forces is directed away from the point of origin of the ectopy, or from the insertion of the bypass tract in the case of W P W

Classifications of W P W by vectorcardiography have described two basic orientations of the initial conduction delay which has a duration varying from 20 to 70 msec. Delays oriented anteriorly were designated as Type A and presumably originated from early activation of the posterobasal wall of the left ventricle. Type B resulting from early activation of the right ventricular free wall produced delta vectors directed to the left.^{20, 21}

In either of these varieties the initial delay could be oriented in a marked superior direction thus mimicking inferior wall infarction.^{21, 22} In addition the Type B delta vector if oriented posteriorly would mimic anterior infarction and the Type A QRS loop oriented largely to the left and anterior of the E point could mimic dorsal infarction or right ventricular hypertrophy.

More recently⁶ the above classification has been expanded. Castellanos and co-workers^{7, 8} have recommended that the right ventricular entrances be subdivided into posterior and anterior types. The anterior entrance type in Type B exhibits a delta vector directed to the left and posterior while in the posterior entrance type the delta vector is directed to the left and slightly anterior to the X axis. In contrast the Type A delta vector is markedly anterior resulting in positive delta and QRS complexes in Leads V₁ and V₂ of the scalar electrocardiogram. Tonkin and associates⁹ made the important observation that all septal bypass tracts produced a superior 10 msec vector in the frontal plane while all free wall bypass tracts resulted in inferiorly oriented 10 msec vectors. Thus determination of the spatial orientation of the initial conduction delay in W P W serves not only to identify the left or right ventricle as the site of entrance but attention to the frontal plane axis may separate free wall from septal bypass tracts. Such identification has important surgical implications.

Following the initial delay of the delta vector activation of the ventricular masses occurs as a fusion complex between the activation wave generated from the bypass site entrance and the normal activation via the His Purkinje system.^{11, 12} If the activation through the normal conducting system dominates the QRS loop after the delta vector may be largely normal.

However if conduction through the bypass tract dominates the conduction through the AV node and His Purkinje system a delayed varying degrees of fusion complexes occur producing the electrocardiographic concertina effect described by Portillo.¹³ If activation occurs entirely through the bypass tract conduction delay is evident throughout the entire QRS loop which becomes greatly prolonged. In the case of Type pre-excitation the terminal delay will be oriented to the right but usually posterior and does not resemble the common variety of right bundle branch block in which the terminal delay is oriented to the right and anterior. Similarly Type B with pure bypass tract activation of the ventricles conduction delay will be evident throughout a loop oriented to the left and posterior and which will superficially resemble left bundle branch block.^{14, 15}

An excellent programmed presentation of electrocardiography and vectorcardiography in the W P W syndrome with and without complicating bundle branch blocks was presented by Castellanos and co-workers.² An especially interesting problem is presented by the combination of pre-excitation with bundle branch block.¹⁶ This is a distinctly different phenomenon from the vectorcardiogram produced by complexes representing total excitation via the bypass tract.^{20, 21} In Type A W P W with early excitation of the left ventricle, a coexistent right bundle branch block is perfectly possible. Several patients with early excitation of the left ventricle and coexistent right bundle branch block have been reported, and in others the possibility of this combination was established by artificial catheter induced right bundle branch block.¹⁷ In contrast to the loops resulting from total excitation via a left sided bypass the loops of left sided bypass with right bundle branch block display a distinct right anterior terminal appendage as in the usual forms of right bundle branch block described in an earlier section.

Of great theoretical interest are those cases in which bundle branch block appears to exist in the same ventricle exhibiting the pre-excitation.^{18, 19} A reasonable explanation seems to exist for Type B W P W of the posterior entrance type with coexistent right bundle branch block. Here it seems possible that the posterior entrance leads to activation of the left ventricle via the fascicular system prior to activation of the right ventricle which in turn is aberrant because of the right

horizontal plane with a decrease in duration of the anterior P forces and an \angle axis intercept (crossing point from anterior to posterior) distinctly less than in the normal or in the patient with right atrial hypertrophy.^{2,3}

Recording of P loops in most clinical laboratories requires very careful attention to skin preparation, electrode placement, respiratory phase of recording, careful grounding of patient and equipment, high amplification, and use of one of the techniques to eliminate QRS and T data.

Zoneraich and Zoneraich¹⁰ have opened a new area for vectorcardiographic investigation with their concept of intra atrial conduction disturbances. They have properly pointed out the parallel between the ventricular fascicular conduction system and the very similar internodal connections which join the SA node to the AV node and which pass through the atria. They used extremely high amplification (300 mm per millivolt) and high frequency recording. Using such technology to record normal P loops confirmed the location of the maximum vector as left inferior and posterior as described by other workers and also confirmed the previously observed normal rotation of the P loop as counterclockwise in the frontal and horizontal planes and clockwise in the right sagittal plane. Two small notches were observed in normal patients: one in the efferent and the other the afferent limb. Maximum anterior or posterior voltages were confirmed as less than 0.1 millivolts. Although the Zoneraihs described four different patterns for their patients with intra atrial conduction disturbances, all patterns included many fine notches and bites. These were frequently visible only in the vector display and not in the scalar presentations. Such bites and notches were observed with and without left atrial dilatation as determined echocardiographically. The Zoneraihs hypothesized that the bifid P wave scalar contour may well correspond to a lesion in the Bachmann bundle. The authors comment¹⁰ on the difficulties in assessing the separate contributions of conduction delay, hypertrophy or dilatation to the observed P loop morphology.

Vectorcardiographic studies of patients with atrial arrhythmias have been reported. In low atrial rhythms, either occurring spontaneously or pacemaker induced, an expected shift of the maximum P vector occurs with a displacement to the right (left atrial rhythm) or to the left (right atrial rhythm). The rotation of the P loops in

the frontal and horizontal planes varies according to the site of origin of the P loop and of the first atrium activated. In the presence of inferior or low atrial rhythms, no criteria are presently available for the identification of right or left atrial overload. Vectorcardiography has been obtained in patients with atrial flutter.¹¹⁻¹³ In 55 patients, Zoneraich and co-workers¹¹ described two vectorcardiographic patterns of flutter. One, an elliptical smooth loop, was found in 63% of patients with normal sized left atria and the second was a distorted flutter vectorcardiographic loop with many notches and bites. This occurred in 67% of patients with enlarged left atria.¹¹

Following conversion of flutter patients to sinus rhythm, notches and bites characteristic of intra atrial conduction delay were found in 62% of patients with enlarged left atria and in 43% of patients with normal sized atria by echocardiography. Although the electrical activity in flutter is continuous, masking the onset of activation, correlations with prosthetic valve movement¹⁴ seem to indicate that the onset of left atrial activation and contraction coincides with the rapid superiorly and posteriorly directed forces in the vectorcardiogram. Right atrial activation then follows.

Bartall and associates¹⁵ have studied the vectorcardiography of atrial fibrillation using timed loops. Their criterion for detecting left atrial enlargement was a maximal VCG F wave exceeding 0.12 millivolts. This was found in 25 of 38 subjects (66%). However, only 10 of the 38 patients with atrial fibrillation had electrocardiographic F waves exceeding 0.1 millivolts in amplitude as measured in Lead V. Of the 25 patients with increased F wave voltage by vectorcardiogram, 21 had large left atrial dimensions by echocardiography. Although the timed horizontal plane vectorcardiogram appears to be superior to Lead V of the electrocardiogram in atrial fibrillation in identifying enlargement of the left atrium, additional explorations of this interesting area appear indicated.

Wolff Parkinson White syndrome (references 2 to 16, 290 to 303)

The vectorcardiography of QRS complexes in the W P W syndrome bears certain resemblances to the vectorcardiography of QRS complexes from ectopic ventricular sites. In both types of loop, the initial forces are inscribed with conduc

predicting not only the location of akinetic or dyskinetic segments after myocardial infarction but it has some value in predicting the extent of such dysfunction

11 Vectorcardiography has some of its greatest diagnostic value in patients with left bundle branch block. Valuable clues to the presence of infarction in various areas as well as to right ventricular hypertrophy may be obtained

12 The vectorcardiography of pacemaker induced QRS complexes may strongly suggest the presence of underlying myocardial infarction. A change in direction of the vectorial direction of the pacemaker spike itself may be a clue to wire fracture

13 High amplitude vectorcardiography of the P waves is a strong diagnostic tool in the recognition of right or left atrial overloads and is probably the best method available for the detection and evaluation of intra atrial conduction disorders

14 T loop vectorcardiography is of value in identifying unexpected rotations or speed of inscription which may frequently be a clue to ischemic disease in addition to identifying a secondary T abnormality as in bundle branch blocks

15 In children with the Wolff Parkinson White syndrome vectorcardiography provides valuable clues to the diagnosis of congenital heart disease

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bundle branch block. Although some cases of Type A pre-excitation coexisting with apparent bundle branch block have been described, this has never been reproduced experimentally, and even the authors have no satisfactory explanation for the phenomenon.¹⁰ Fortunately, this last one is very rare.

The diagnosis of myocardial infarction with Wolff-Parkinson-White syndrome is merely difficult if not impossible. In one paper,¹¹ a patient with myocardial infarction had intermittent W-P-W syndrome. The infarction abnormalities were totally obscured by the aberrant nature of the early forces when pre-excitation was present, although they were very visible with normal conduction.

In one little-recognized area, the recognition of congenital heart disease, vectorcardiography may play a significant role. In the presence of W-P-W, Miller and Victorica^{12,13} have described the importance of the relationship between the delta and the main QRS axis in children suspected of congenital heart disease. When these axes are more or less parallel, congenital heart disease is usually absent. For example, a Type A pre-excitation with an anterior QRS loop or a Type B with a posterior QRS loop would be more consistent with the absence of congenital heart disease. However, when these vectors are opposite in direction, congenital heart disease was generally found. Further, the displacement of the major or mean QRS vector is generally oriented as expected for the appropriate ventricular hypertrophy. Thus, a posterior QRS vector in the presence of anterior delta vector suggests left ventricular hypertrophy. In contrast, right ventricular hypertrophy is more likely when the mean QRS is anterior despite a posterior delta vector in W-P-W Type B. An interesting exception of this general rule is found in Ebstein's abnormality of the tricuspid valve. Here, Type B (posterior delta vector) is commonly found, but the major QRS axis is also posterior. In these patients, the delta vector is also oriented in a superior direction.

Indications for vectorcardiography

1 In the evaluation of clinically normal patients who have abnormal electrocardiograms, especially apparently increased or decreased anterior forces, the vectorcardiogram may be entirely normal, confirming the clinical impression.

2 In the evaluation of chest pain problems with an apparently completely normal electrocardiogram, a T-loop study may disclose abnormal rotation of a wide but left and anterior horizontal loop. This excellent sign of lateral ischemia may be completely hidden in the scalar record.

3 Although high QRS voltage is better detected by scalar ECG criteria than by vectorcardiographic or the orthogonal lead criteria, the separation of right or left ventricular hypertrophy from combined hypertrophy is better accomplished by vectorcardiography.

4 The vectorcardiogram is valuable in the differential diagnosis between pulmonary emphysema and anterior infarction.

5 The vectorcardiogram is valuable in confirming the presence of abnormally large anterior QRS forces and is particularly helpful in separating patients with right ventricular hypertrophy from patients with true dorsal infarction. However, it must be always remembered that anterior conduction delay, Wolff-Parkinson-White syndrome, and hypertrophic and other cardiomyopathies may produce an identical picture. Multiple myocardial infarctions are best recognized in the vectorcardiogram, particularly when combined with bundle branch block or divisional block.

6 The vectorcardiogram may also be of value in identifying the site of entrance of a bypass tract as free wall or septal in Wolff-Parkinson-White syndrome.

7 Right ventricular hypertrophy is frequently easily diagnosed by vectorcardiography when it is only suspected in the conventional electrocardiogram.

8 The diagnosis of right ventricular hypertrophy combined with right bundle branch block is frequently possible by vectorcardiography, although care must be taken to avoid false positive diagnoses. The combinations of right bundle branch block with inferior or superior divisional block are readily evident in the vectorcardiogram.

9 With vectorcardiography, it is possible to diagnose inferior infarction even in the presence of initial inferior forces which produce positive deflections in Leads II and aV₁ of the scalar electrocardiogram. Further, it is possible to diagnose anterior infarction even in the presence of initially positive deflections in the right precordial leads.

10 The vectorcardiogram may be of value in

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tricular premature beats, ventricular tachycardia and fibrillation as well as atrioventricular conduction disturbances have been reported to occur with phenothiazine therapy.^{5, 10, 13, 14}

Kelly and co-workers⁵ reported fatal heart block and ventricular tachycardia in two patients treated with large doses of thioridazine and Desautels and associates¹⁴ reported a case of non-fatal ventricular tachycardia. In 1965, Hollister and Kosek described six cases of sudden death in the absence of cardiac disease following phenothiazine treatment. In all six patients a syncopal seizure episode was immediately followed by cardiorespiratory arrest. In one case resuscitation was temporarily accomplished and irreversible ventricular fibrillation was documented on the electrocardiogram. These patients were all receiving drug in the acceptable therapeutic dose range.¹²

Lesstma and Koenig¹⁵ reported fatal ventricular tachycardia in a 24-year-old female treated with chlorpromazine, thioridazine and stelazine. Unexpected death in 12 patients receiving phenothiazine drugs was reported by Moore and Book.¹⁶ No adequate anatomic explanation for death was found in these cases and the ECGs were not available. Death associated with ventricular arrhythmia was reported by Giles and Modlin¹⁷ in a 19-year-old male. The fatal event followed repolarization changes seen on the ECG tracing and bouts of ventricular irritability.¹⁷

Alexander and Nino³ described tachycardia and left bundle branch block in a 36-year-old asymptomatic man who was treated with phenothiazines. However, this patient received concomitant tricyclic antidepressant therapy which can also cause conduction disturbances.¹ Fowler and colleagues¹⁸ in 1975¹⁹ described electrocardiographic changes and cardiac arrhythmias in eight patients treated with psychotropic drugs. Although most patients received more than one drug, thioridazine seemed to be responsible for ventricular tachycardia in five of these eight patients and one of these episodes was fatal in a 35-year-old female. Supraventricular tachycardia was seen in one patient on chlorpromazine.

The pathogenesis of phenothiazine-induced rhythm disturbances is still unknown. Prolongation of the Q-T-U interval has been demonstrated to be associated with ventricular arrhythmias.^{19, 20} Prolongation of the QT interval by phenothiazines suggests an increased duration of ventricular refractoriness and a low threshold for

multiple ventricular responses and ventricular fibrillation.^{10, 21} It is known that phenothiazines have a vagolytic effect and elevate plasma catecholamine levels which also may explain its arrhythmogenic effects.

Lesions in the central nervous system particularly in the brainstem can affect the ECG repolarization process.²² The effect of phenothiazines on the ECG may be related to their profound action on the brainstem. It is also possible that the microscopic intramyocardial lesions described in some patients treated with phenothiazines might be the basis for the abnormal electrocardiograms.^{5, 6}

Although there is a slight risk of arrhythmia with therapeutic doses of phenothiazines, these drugs have well-documented antiarrhythmic effects.^{3, 23} In experimental animals, thioridazine caused a significant reduction of acetylcholine-induced atrial fibrillation as well as a reversion of atrial fibrillation to normal sinus rhythm.²⁴ In addition, this agent caused a long-lasting suppressor action on ventricular ectopic tachycardia produced by two-stage coronary ligation. The quinidine-like properties of phenothiazines contribute to the antiarrhythmic activity of these drugs.

Hemodynamic effects of phenothiazines

A powerful vasodilator action has been demonstrated with chlorpromazine.³ This vasodilator effect is caused by the blockade of peripheral adrenergic receptors and a direct action of the drug on the smooth muscle of the arterial wall. In addition, the drug has a central nervous system effect which contributes to its vasodilator activity. Chlorpromazine has also been shown to have a direct depressant action on the myocardium.¹

Effects on blood pressure

As a result of the peripheral vasodilatory and negative inotropic effects of phenothiazines, hypotension is the most common side effect seen in patients without congestive heart failure. After several weeks of chronic therapy, patients develop tolerance to the hypotensive effects of the drug and blood pressure returns to near normal levels. However, in some patients a certain degree of orthostatic hypotension persists. This adverse effect is more commonly seen with chlorpromazine and thioridazine than with the piperazine derivatives.¹

appraisal and reappraisal of cardiac therapy

ited by Arthur C. DeGraff and Julian Frieden

effects of phenothiazines

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The phenothiazines are widely used drugs in medicine today. In fact there are more than two dozen phenothiazine compounds being used in medical practice.¹ Chlorpromazine (Thorazine) and other phenothiazine derivatives are employed primarily in the treatment of patients with psychoses. However they are also important antiemetic agents and some phenothiazine preparations are now being used for their antihistamine and analgesic effects as well.

Experimental and clinical observations have demonstrated that phenothiazines have significant electrophysiologic and hemodynamic effects which may be of clinical importance. The state of knowledge regarding the cardiovascular effects of phenothiazines will be reviewed.

Electrophysiology and effects on the electrocardiogram

Experimental evaluations in animals demonstrated a significant effect of phenothiazines on the action potential of isolated atrial and ventricular muscle as well as Purkinje fibers. Anta and Surawicz² showed that phenothiazines reduced membrane responsiveness by decreasing the maximal rate of rise of phase 0 of the action potential. The psychotropic drugs also cause a decrease in the amplitude of phase 2 as well as a reduction in the rate dependent change in the duration of this phase. Phase 3 was found

to be prolonged following phenothiazine administration. The electrophysiologic properties of phenothiazines are similar to those reported for quinidine.³ This explains the similar effects of phenothiazines and quinidine on the surface electrocardiogram.

In man the earliest electrocardiographic change produced by phenothiazines is lengthening of the QT interval which is accompanied by widening, blunting and notching of the T wave.⁴ These changes reflect the disturbances in ventricular repolarization and were found by Huston and Bell⁴ in 53 of 106 (50%) hospitalized psychiatric patients receiving therapeutic doses of phenothiazines. This study and others suggest that the T wave changes are benign. Increasing doses of phenothiazines produce lowering and inversion of the T wave. The ST segments are usually not affected but may be depressed.⁵ These drugs can prolong the PR and QRS intervals but have no effect on the P wave. Electrocardiographic changes occur most commonly after the therapeutic administration of thioridazine are less pronounced after therapeutic doses of chlorpromazine and even less common after trifluoperazine.^{6,7}

The degree of electrocardiographic repolarization abnormality secondary to phenothiazine ingestion appears to be dose related. 200 mg per day of thioridazine can sometimes be associated with detectable ECG changes while these changes occur more consistently with doses exceeding 800 mg per day.^{8,9}

Arrhythmogenic activity and antiarrhythmic effects of phenothiazines

Various arrhythmias have been attributed to the effects of phenothiazine therapy. The arrhythmogenic effects of phenothiazines like quinidine can occur with therapeutic doses.¹ Sinus tachycardia, atrial fibrillation and flutter ven-

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dynamic effects of intravenous chlorpromazine immediately after open heart surgery in 24 patients with high mean arterial pressures. The average intravenous dose of 10.3 mg resulted in a significant decline in systemic blood pressure, right and left atrial pressures, and the pulmonary artery pressure. There was no significant change in stroke volume; however, cardiac output increased secondary to a significant rise in heart rate. Chlorpromazine therapy caused a marked fall in both systemic and pulmonary vascular resistances.

Hemodynamic effects on chlorpromazine in heart failure due to acute myocardial infarction

Significant beneficial effects on the hemodynamic profile were demonstrated by Elkayam and co workers³⁴ in 12 patients with acute myocardial infarction complicated by congestive heart failure. The administration of 25 to 275 mg of chlorpromazine given as an intravenous bolus in increments of 25 mg repeated every 5 minutes was followed by a significant reduction in systemic vascular resistance and in mean capillary wedge pressure³⁴ (Figs 1 and 2). The drug also produced a marked elevation of cardiac output without a significant change in heart rate and mean stroke work index. Although the administration of chlorpromazine resulted in a mean blood pressure fall of 18%, the transmural pressure gradient was not affected (Fig 2). The hemodynamic improvement was also accompanied by a dramatic increase in urine output. Chlorpromazine therapy evoked a considerable degree of sedative effect and a decrement in motor activity in most of the patients.

Cardiogenic shock

Dietzman and Lillehei⁷ advocated phenylephrine, benzamine, and chlorpromazine for treatment of cardiogenic shock. They reported a reduction of the vasoactive response which results from an increase in circulating and tissue levels of catecholamines in patients with cardiogenic shock. This vasodilatory effect of chlorpromazine mediated by the alpha adrenoceptor blockade of the pre and post capillary arteries and venules of the skin and viscera improved tissue perfusion and metabolism. The authors concluded that this effect caused a decrease in morbidity in some patients.

Data by Gulotta in 1970³⁵ and from Elkayam

and co workers in 1977³⁴ also described the beneficial effect of chlorpromazine in the low cardiac output syndrome associated with open heart surgery and cardiogenic shock due to acute myocardial infarction.

Summary

Phenothiazines have significant electrophysiologic and cardiocirculatory effects. The electrophysiologic effect of these drugs is similar to that reported for quinidine. Phenothiazines decrease the rate of rise of phase 0 of the action potential, decrease the duration and amplitude of phase 3, and prolong phase 4. The surface ECG changes produced by phenothiazines are lengthening of the QTc interval, ST-T wave changes, increase in size of U waves, and prolongation of the P interval. The degree of repolarization abnormalities secondary to phenothiazines seems to be dose related.

Various arrhythmias have been attributed to the effect of phenothiazine therapy, and numerous cases of sudden death as a result of fatal arrhythmia have been described. Paradoxically, phenothiazines such as chlorpromazine and thioridazine also have been shown to have significant antiarrhythmic properties. Chlorpromazine shows a powerful vasodilatory effect which is caused by alpha adrenergic receptor blockade, central action, and a direct effect on the vascular wall. In addition, the drugs also have a direct depressant effect on the myocardium. As a result of peripheral vasodilatation and negative inotropic effects, hypotension is the most common adverse reaction of phenothiazines in patients with no evidence of congestive heart failure.

Experimental studies have demonstrated significant reductions in systemic and pulmonary vascular resistance as well as systemic blood pressure following intravenous administration of chlorpromazine. These hemodynamic changes were accompanied by significant increase in cardiac output in one study and by no change in cardiac output in another study. The vasodilatory effect of chlorpromazine resulted in increased renal and mesenteric blood flow and prolongation of survival time in dogs following hemorrhagic hypotension. Chlorpromazine was found effective in relieving abnormal vascular tone and improving the circulation in patients undergoing cardiopulmonary bypass surgery. In patients with myocardial infarction complicated by congestive

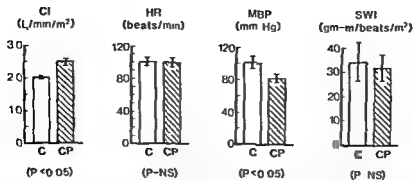


Fig 1 The effects of intravenous chlorpromazine (CP) vs baseline no therapy (C) on cardiac index (CI) heart rate (HR) mean systemic blood pressure (MBP) and stroke work index (SWI) in 17 patients with congestive heart failure due to acute myocardial infarction. The values are presented as means \pm standard errors, NS = not significant (Reproduced by permission from Chest 72:673-677 1977)*

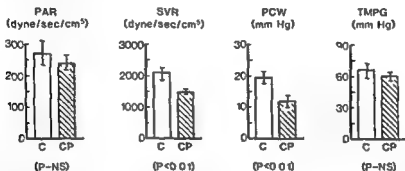


Fig 2 The mean effects of intravenous chlorpromazine (CP) vs baseline no therapy (C) on pulmonary arterial resistance (PAR) systemic vascular resistance (SVR) pulmonary capillary wedge pressure (PCW) and transmural cardiac pressure gradient (TMPG)

Effect on systemic and pulmonary circulation

Goldberg and associates¹ examined the effects of chlorpromazine on the pulmonary and systemic circulation in dogs. The administration of an intravenous dose of 1 mg/kg produced a striking increase in cardiac output and a marked decrease in pulmonary vascular resistance. The systemic vascular resistance and systemic blood pressure also fell significantly with no significant change seen in the heart rate.

Similar experiments performed by Maxwell and co workers² demonstrated somewhat different results. Using 1 mg/kg of chlorpromazine heart rate increased significantly and was accompanied by a marked reduction in systemic vascular resistance. These changes were accompanied by a significant fall of systemic blood pressure and no change in cardiac output.

Hemorrhagic shock

Inglis and associates³ have demonstrated prolongation of survival time in dogs treated with small intravenous doses of chlorpromazine following

hemorrhagic hypotension. Chlorpromazine increased renal blood flow and glomerular perfusion and significantly improved the renal medullary circulation.³ The beneficial effect of chlorpromazine on the renal circulation was accompanied by an improvement in cortical and medullary metabolism⁴ and was associated with an increase in measurable diuresis during low levels of blood pressure. The administration of chlorpromazine was also associated with a marked elevation of the mesenteric blood flow at an arterial blood pressure of 30 mm Hg.

Cardiac surgery

Lemieux and colleagues⁵ have demonstrated the effectiveness of chlorpromazine in relieving abnormal tone of blood vessels in 30 patients undergoing cardiopulmonary bypass surgery. The administration of the drug was associated with increased perfusion as indicated by an increase in percent oxygen saturation of venous blood and in urine output.

Stinson and colleagues⁶ studied the hemody-

Limited pressure control to "optimum" levels may reduce the rate of myocardial infarction in hypertensive subjects

For more than 20 years it has been clear that therapeutic reduction of the blood pressure in hypertensive subjects dramatically lessens their increased liability to illness and death from left ventricular failure, renal damage, and hemorrhagic stroke, while failing to make any incontestable impression upon their similarly heightened susceptibility to myocardial infarction and sudden cardiac death. The general reaction to this seeming paradox has been one of pained disbelief followed by renewed determination to squeeze the pressure down still further. After all, close relationships can be demonstrated between hypertension and premature arteriosclerotic degeneration involving the blood supply to various other organs. Why should the coronaries be different? Such reasoning makes the unjustified assumption that the effects of pressure change within the arteries supplying the brain and kidney must be the same as those created within the nutrient circulation of the heart. It also takes no account of the extent to which high blood pressure should be reduced. Surprisingly little attention has been paid to this important question and still less to another that is even more fundamental: What is the mechanism whereby hypertension increases the infarction rate?

It has long been thought to do so by favoring coronary atherogenesis. The doctrines of pressure normalization and of early treatment in the young rest upon this widespread belief. Yet the best that can be said for it is that the Framingham studies have shown a rising parallel between hypertension and the clinical manifestations of coronary heart disease. This association has been readily accepted as proof that hypertension plays a significant role in the pathogenic processes within the coronary vessel walls. The inference is ill-founded. High blood pressure tends to precipitate angina and myocardial infarction in the presence of pre-existing coronary atheroma whatever its origins. Rather is there good reason to accept Pickering's view that hypertension is only weakly correlated with coronary atheroma, in this differing from the rest of the arterial circulation, no doubt for the reason that the structural and functional characteristics of the heart are themselves unique. In an angiographic assessment of risk factors for atheroma in 173 patients with and without coronary atheroma, the vessels being accounted as normal, moderately or severely atherosclerotic, Frick and his colleagues found that the difference in the prevalence of hypertension did not reach statistical significance in any comparison between the groups.¹

In a pathological study of patients dying of congestive heart failure, Davis and Klauser found marked coronary artery disease in 23 out of 26 patients without hypertension and in only 26 out of 49 patients with hypertension. Later, Harrison and Wood concluded that the coronary arteries vary sharply between hypertensive and ischaemic cases: in the former they

are large with smooth bores, in the latter they are narrow, frequently occluded. Progression studies in coronary atheropathy and experimental physiology² have pointed to the same conclusion.

There remains however a second possibility. Much research has indicated that there may be important relationships between hypertension, mental and physical stress, particularly isometric stress, sympathetic overactivity, catecholamine circulation, and potentially lethal arrhythmias.³⁻⁵ This work is interesting in the context of observation made by Berglund and colleagues. In an analysis of the rate of nonfatal myocardial infarction sustained by hypertensive patients under treatment as compared with in controls, they noted that a significant benefit from pressure reduction occurred early and continued throughout follow-up. So swift a response suggests the preemption of infarction threatened by a precipitating rather than by a long factor. A surge of very high pressure could be such a factor.

It may be then that hypertension increases the risk of infarction and sudden cardiac death largely by the occasional precipitation of these events, rather than by any significant influence upon coronary pathogenesis. But if this be so, has beta blockade, with its promise of cardioprotection, brought no clearly recognizable improvement? A recent study has suggested a possible answer to this question.⁶

In a survey of middle-aged severe essential hypertensive subjects, most of them male, followed under treatment over a mean period of more than six years, the final observed diastolic pressures (FDPs) as last recorded before the moment of infarction or its avoidance in the patients who suffered first myocardial infarction were compared with those in the patients who had avoided it. There were no statistically significant differences between the two groups in the values for the other main coronary heart disease (CHD) factors. But the relative risk of myocardial infarction, sudden cardiac death in the patients with FDP reduced to < 90 mm Hg (Phase IV) was more than five times greater than in the patients with FDP in the range of 100-119 mm Hg ($P < 0.01$), the difference falling off with FDP about 110 to 114 mm Hg (Table I). This bimodality is further illustrated by incidence comparisons between three major ranges of FDP—76 to 91 mm Hg, 95 to 109 mm Hg, and 110 to 140 mm Hg. The ratios of patients with infarctions to numbers in each range were respectively 16 of 41, 4 out of 58, and 15 out of 70. Only in those whose FDP levels remained above 120 mm Hg did a clearly increased level of infarction begin to reappear. Other arteriovascular complications were somewhat less than expected from patients under treatment despite relatively modest individual falls in many of them.

Moreover, in those who had developed an infarction

heart failure intravenous administration of chlorpromazine caused significant hemodynamic improvement and a considerable degree of sedation. The drug was found effective in reducing the vasoactive response in patients with cardiogenic shock which resulted in improved tissue perfusion and metabolism.

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Exercise and recurrence of myocardial infarction

The hypothesis that vigorous exercise rehabilitation is of benefit to patients following myocardial infarction is currently being tested in Southern Ontario using a stratified randomized controlled trial. To date 50 of the 751 patients have been followed to the point of reinfarction and the resultant data has now been analyzed seeking clues to those individuals with an above average risk of a further coronary event.

The most striking feature of this survey is the similarity of patients who infarct and those who do not. While the Southern Ontario multicenter sample included some individuals who had a slow progressive extension of their disease in many individuals the second infarction (like the first) occurred with little clinical or physiological warning. This may reflect the nature of patients referred for exercise rehabilitation all were by selection under 54 years of age while the exercise program may have attracted cases with a relatively mild initial episode and/or a fairly complete restoration of myocardial function.

The only clinical clue to the likelihood of reinfarction gained from the patients initial records was a history of multiple infarctions. Characteristics of the initial attack (symptomatic ECG changes enzyme changes cardiac arrest dysrhythmia and minimum systolic blood pressure) did not modify subsequent prognosis. Presumably residual myocardial function is more crucial than the characteristics of the previous acute episode. The referral process and criteria of

admission to the multicenter trial may also have sorted out a relatively uniform type of patient suited to exercise with an infarct of less than average severity.

The most important adverse finding on admission to the trial is exercise non compliance. Total drop outs have a risk of recurrence more than 20 times the average and limited exercise participation also increases risk by a factor of at least five. Is this because advanced disease and poor myocardial function keeps some patients from performing the prescribed exercise? Residual disability shortness of breath and angina all increase the chances of recurrence but nevertheless cardiac problems are rarely cited as a reason for non compliance. It is possible that those who fail to exercise are missing a therapeutic benefit of vigorous exercise but this again is doubtful since the figures from Southern Ontario and other trials to date suggest no advantage of high intensity exercise relative to homeopathic recreation or inactivity. The most probable explanation is that exercise non compliance is serving as a marker of a generally adverse life style. Many studies have shown the linkage between poor exercise compliance, persistent smoking and obesity. Rechnittzer and colleagues (unpublished data) have also noted that a combination of Type B personality a blue-collar job and vigorous exercise yield a poor prognosis. Finally the group with recurrent infarction shows an above-average proportion of subjects engaged in commerce with a deficit in professional and managerial work.

Signs of a poor prognosis include cardiac enlargement aneurysm polyfocal ventricular premature beats exercise ST segmental depression and a serum cholesterol > 270 mg/dl. The importance of deteriorating myocardial function is at

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Table 1 Relative risks of myocardial infarction in ascending subgrades of FDP*

| FDP (mm Hg) | Patients | Events | Relative risk | p |
|-------------|----------|--------|---------------|--------|
| < 90 | 18 | 7 | 54 | < 0.01 |
| 90-99 | 39 | 4 | 14 | NS |
| 100-109 | 49 | 3 | 10 | — |
| 110-119 | 55 | 11 | 33 | < 0.1 |
| 120+ | 15 | 2 | 19 | NS |

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FDP \leq 90 mm Hg the pressure falls were all markedly greater than in unaffected controls matched for CHD risk factors that included form of treatment age sex and established pretreatment diastolic pressure.

These findings suggest that in severe middle aged hypertensive subjects attempts at normalization of the pressure may precipitate as many infarctions as it prevents perhaps cancelling out a lessened incidence at high levels a concept that is supported by an acknowledgment from Berglund and colleagues that in their study on the effects of treatment the percentage of well controlled patients after 2 years treatment was indeed low despite their lessened infarction rate compared with that of the untreated.

All this constitutes a challenge to the popular concept of good control. But it can scarcely be accounted surprising. Misled by mean values and persuaded by those who would have it that hypertension is a potent cause of coronary atheroma clinicians throughout the world have continued to pay lip service to the proposition that reduction of blood pressure to normal levels should diminish the incidence of myocardial infarction in hypertensive patients. Yet there is no convincing evidence that hypertension significantly favors coronary atherogenesis nor that lowering systemic pressure can arrest it. Certainly the prospect of longevity as shown by actuarial tables is improved by a blood pressure that has continued or possibly (as remains to be seen) has always been controlled at a normal level. But this simple epidemiological appreciation takes no account either of the individual patient or of the site of the fatal lesion. Some 30% of middle aged Englishmen and no doubt many more such men who have adopted the life styles of the Western type civilization whether hypertensive or not already have advanced coronary artery disease often unsuspected. It is easy to believe that severe continued reductions in their systemic arterial pressure unprompted fortuitously upon the constantly changing mechanisms of auto-regulation may sometimes lead to disastrous failures of coronary perfusion, perhaps with stasis and platelet aggregation the risk made all the greater by the diverse and frequently unpredictable modes of action of the hypotensive drugs concerned. Such combinations of drug and circumstance have already been shown to precipitate myocardial infarction in patients under close observation in hospital.

For many reasons the clinical reduction of blood pressure is an imprecise exercise. Even when aimed at levels well above normality it may still occasionally overshoot the mark to a degree that threatens critical and possibly fatal, myocardial ischaemia. Thus it may well be that in its treatment no less than in its natural history hypertension presents a dual threat of infarction and sudden cardiac death by precipitation

of these events at each extremity of the pressure scale. This threat should be avoidable in both its forms if "good control" be taken to imply not normality, the standardized average for age and sex but a decrease in pressure sufficient to restrain hypertensive injury to target organs, including the heart while avoiding such hypotension as may set off infarction.

In 1957 it was suggested that "even a limited depression of the blood pressure could be as effective as the most exacting control." Today it would seem reasonable to conclude that at least in severe hypertensive subjects the policy should be one of reduction into an optimum range calculated as far as possible for the individual that is likely still to be considerably above that of normalization after induced pressure falls of perhaps no more than about 22" or to a diastolic pressure of around 104 to 110 mm. Hg.

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Exercise and recurrence of myocardial infarction

The hypothesis that vigorous exercise rehabilitation is of benefit to patients following myocardial infarction is currently being tested in Southern Ontario using a stratified randomized controlled trial. To date 50 of the 751 patients have been followed to the point of reinfarction and the resultant data has now been analyzed seeking clues to those individuals with an above average risk of a further coronary event.

The most striking feature of this survey is the similarity of patients who infarct and those who do not. While the Southern Ontario multicenter sample included some individuals who had a slow progressive extension of their disease in many individuals the second infarction (like the first) occurred with little clinical or physiological warning. This may reflect the nature of patients referred for exercise rehabilitation all were by selection under 54 years of age while the exercise program may have attracted cases with a relatively mild initial episode and/or a fairly complete restoration of myocardial function.

The only clinical clue to the likelihood of reinfarction gained from the patient's initial records was a history of multiple infarctions. Characteristics of the initial attack (symptomatology, ECG changes, enzyme changes, cardiac arrest, dysrhythmia and minimum systolic blood pressure) did not modify subsequent prognosis. Presumably residual myocardial function is more crucial than the characteristics of the previous acute episode. The referral process and criteria of

admission to the multicenter trial may also have sorted out a relatively uniform type of patient suited to exercise with an infarct of less than average severity.

The most important adverse finding on admission to trial is exercise non-compliance. Total drop-outs have a risk of recurrence more than 20 times the average. Limited exercise participation also increases risk by a factor of at least five. Is this because advanced disease and poor myocardial function keeps some patients from performing prescribed exercise? Residual disability, shortness of breath and angina all increase the chances of recurrence. Nevertheless cardiac problems are rarely cited as a reason for non-compliance. It is possible that those who fail to exert are missing a therapeutic benefit of vigorous exercise but again is doubtful since the figures from Southern Ontario and other trials to date suggest no advantage of high intensity exercise relative to homeopathic recreation or activity. The most probable explanation is that exercise non-compliance is serving as a "marker" of a generally adverse life-style. Many studies have shown the linkage between exercise compliance, persistent smoking and obesity. Rechnitzer and colleagues (unpublished data) have also shown that a combination of "Type B" personality, a blue-collar, and vigorous exercise yield a poor prognosis. Finally the group with recurrent infarction shows an above average proportion of subjects engaged in commerce, with a deficit in professional and managerial work.

Signs of a poor prognosis include cardiac enlargement, aneurysm, polyfocal ventricular premature beats, exercise segmental depression and a serum cholesterol > 200 mg/dl. The importance of deteriorating myocardial function is also

Principal investigators are G Andrew C, Buck D, Cunningham N, Jones, T, Kavanagh, N, Oldridge J, C, Farkas H, Rechnitzer S, Sangal, R, J, Shephard, J, Sutton and M Yuhasz. Associate investigators are F Berkman, H Demers, R Fowles, P Miles, B Morton, P Tjorlor and R Timmings.

ested by the inability to develop a normal rise of systolic blood pressure during exercise. Nevertheless, physiological response to exercise does not show major differences in those who sustain reinfarction. Possible warnings include a low stroke output relative to work rate, a widened arteriovenous oxygen difference and poor matching of ventilation and perfusion. None of these indicators are very clear-cut presumptions because recurrent disease includes both cases of sudden cardiac dysrhythmia and individuals who develop progressive pump failure.

With the possible exception of exercise non-compliance, the ratios for the various warnings we have discussed are too low to be of great value in advising individual patients. The safety of exercise rehabilitation will thus continue to depend upon a cautious initial prescription of exercise, gradual progression and temporary restriction of activity in the face of adverse symptoms.

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Giant cell arteritis—a cardiological blind spot?

Few would disagree that the cardiologist has been faced with and has overcome several major challenges in his field during recent decades. One which remains and unfortunately appears to have been largely ignored is that presented by giant cell arteritis (GCA). Thus Pavley recently asked the question: "What, then is happening to the bulk of these patients referred to cardiologists who it seems are either seeing this disorder and not diagnosing it or diagnosing it but not reporting it?" Our clinical experience, a survey of publications, and the lack of reference to GCA in major cardiological texts all suggest that the former situation is more prevalent. Indeed with GCA diagnostic delays or failures permeate well beyond the boundaries of cardiological practice and undoubtedly occur more frequently than is generally appreciated within every major subspecialty of internal medicine.

Although GCA may cause angina pectoris, myocardial infarction, aortic regurgitation, aortic dissection, congestive cardiac failure, perhaps pericarditis, and even simulate infective endocarditis, its prevalence in cardiological practice is

unknown. Recognition that arteritis may be the underlying cause of these cardiac events during life is by no means easy, demanding a high index of suspicion and awareness of the deceptive natural history of the disease. Yet there are data indicating that GCA is by no means a rare disease affecting more than one per cent of the elderly Caucasian population. The dominance however of atherosclerosis in the league of diseases in Western countries has generated complacency with regard to consideration of less commonly seen disorders such as this arteritis.

It has become increasingly apparent that GCA is a chronic disease of varying severity and fluctuating course extending over a few to as many as 10 to 15 years. While temporal arteritis is easily diagnosed events such as unexplained anemia, pyrexia of undetermined origin, malaise, depression or a negative laparotomy for possible malignancy any of which may have occurred months or years earlier are presentations to which the cardiological mind is not often attuned. Nevertheless, these may be the only clues indicating the true cause

Effective coronary care and mortality rates

To the Editor

May I refer to your Editorial 'Home or hospital for myocardial infarction—who cares?' This is based on the Nottingham study reported in 1978. I would like to point out the limitations of this study. It was carried out over a four year period and covered a population of approximately 100 000. From the expected incidence of myocardial infarction some 1,200 cases would have been anticipated among that population over the four year period. Two hundred and sixty four patients suspected of having a myocardial infarction were randomized. However only 150 of these had a definite or probable myocardial infarction and were randomized to home or hospital treatment. Thus of the patients likely to have had a myocardial infarction only 12.5% were randomized. This is remarkable in that the Nottingham workers point out that one of the major defects of the Bristol study was the small proportion of patients who were randomized.

From their study the Nottingham workers concluded that "For the majority of patients to whom a general practitioner is called because of suspected infarction hospital admission confers no clear advantage." Yet in their study over 40% of the patients with suspected myocardial infarction had contacted their doctor within one hour of the onset of symptoms and nearly 60% within two hours. Nevertheless the average time from the onset of symptoms to the mobile team's arrival with the patient was three hours and a further two hours elapsed prior to randomization. It may be concluded that in the Nottingham study there was a larger administrative delay than patient delay. The authors record that during the time between the patient's call for help and the arrival of the mobile team 14 patients died, presumably suddenly and from ventricular fibrillation. A further seven patients developed ventricular fibrillation after arrival of the team, yet only three of these seven survived six weeks. Seventy three percent of the patients managed by the Belfast unit who developed ventricular fibrillation outside hospital after the mobile team's arrival survived to leave hospital. The standard of coronary care received by the patients in Nottingham both outside and inside hospital must be questioned since it is reported that patients on admission to the coronary care unit come under the care of a general physician on duty that day. The head of the unit considers his role to be that of an administrator and educator. The junior doctors manning the mobile coronary care unit are drawn from the general medical units of the hospital.

In the Editorial the authors state that "76% of patients seen by the team were suitable for care at home." Yet among those patients with a final diagnosis of definite or probable myocardial infarction who were excluded from randomization the six week mortality rate was 37%. No explanation for this very high mortality rate is given.

The Nottingham data show the obvious. If patients are seen late after the onset of symptoms the effect of coronary care will be minimal. Despite the evidence from Belfast and Seattle Hampton and Nicholas conclude that mobile coronary care units as at present envisaged will not appreciably

affect mortality from heart attacks. This conclusion is dangerously erroneous and has already inhibited the development of prehospital coronary care schemes in Britain so apparently the policy of the Department of Health is based on the Nottingham propaganda. Sadly therefore there will continue to be 5 000 unnecessary deaths annually in the United Kingdom.

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Reply

To the Editor

Doctor Adgey is of course entitled to state her own opinion on our published work but what she should not do is attempt to reanalyze our data in a way which could mislead others. May we suggest that your readers should scrutinize the original paper on which our Editorial was based. They can then form their own opinions and can judge for themselves the validity of Doctor Adgey's comments.

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Of senile anemia

Old patients with or without active heart disease regularly with chronic anemia. It is important that the general health of the patient with heart disease always be considered not only because associated diseases contribute to the patient's symptom complex but also because some associated diseases affect the heart directly and/or indirectly. This is certainly true of anemia. When the concentration of red cells and hemoglobin is low, the oxygen transport buffer mechanism, and other important functions of hemoglobin and erythrocytes are impaired, and the myocardium suffers as a consequence.

Heart disease is especially common in older people. It is well to realize that many old people have chronic anemia for which the etiology remains unknown. Even after extensive hematologic study with all available methods, the cause is not established satisfactorily. The anemia may vary from mild to severe. Yet the use of all therapeutic measures and agents fails to modify it except for the temporary influence of transfusions. But transfusions can be dangerous in that they may precipitate congestive heart failure in people with heart disease when transfusions are not used properly and cautiously.

This type of chronic anemia of "unknown" cause in old people may be called "senile anemia," the anemia of old age, the result of poor function of an old hemopoietic system. Unless the anemia is severe and is contributing to the ill health or to the cardiac disease of the elderly patient, it should be left alone. After all, sluggish and relatively inactive old people do not need as much circulating blood or hemoglobin as young, extremely active people do.

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Table 1 Effect of flow rate on percentage of NTG remaining after passage through polyvinyl chloride infusion set

| Flow rate (ml/min.) | Time (min) | | | | | | | | |
|------------------------|------------|------|------|------|------|------|------|------|-----|
| | zero | 30 | 60 | 90 | 120 | 180 | 240 | 300 | 360 |
| 0.25 | 22.7 | 30.6 | 36.5 | 40.2 | 44.4 | 48.5 | 52.3 | — | 55 |
| 0.50 | 42.6 | 52.8 | 57.6 | 63.9 | 65.1 | 69.0 | 72.2 | 73.8 | 75 |
| 0.75 | 50.0 | 62.3 | 66.9 | 71.4 | 73.5 | 77.2 | 79.9 | 80.9 | 81 |
| 1.00 | 50.7 | — | 69.9 | — | 78.5 | 83.6 | 84.1 | 84.9 | 85 |

but too often we forget that there is something else between the patient and the container—a system that in this very case turns out to be more important!

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Sex and the differential diagnosis of uncomplicated angina pectoris

To the Editor

In a recent publication from a widely respected epidemiological investigational team on the occasion of reporting an extraordinary high percentage of remission of angina pectoris cases first the validity of the acquisition of the anginal symptomatology was questioned and secondly a disturbing distribution between sexes of such patients emerged.

The aim of this paper is not to deal either with the remission rate of this symptom complex or with its eventual significance. The finding however of a 13% preponderance of women ($N = 84$) over men ($N = 74$) in a natural (unselected) population is in fact astounding and not only on theoretical, but also on practical grounds. It was therefore thought to be very constructive to expose briefly the findings of an investigation concerning this matter. We evaluated with the HIP questionnaire for angina pectoris 200 consecutive cases addressed to us with the problem of recurring chest pain. The following groups of cases were not included in the above 200 cases: (1) cases with historical and/or electrocardiographic documentation of old myocardial infarction (2) cases where the electrocardiographic and/or enzymatic follow up was diagnostic of a recent myocardial infarction (3) cases with valvular disease (4) cases with syndromic cardiomyopathies (4) cases with bundle branch block and (5) cases of recent administration of digitalis preparation. (The last two prerequisites were

set because of a parallel study of the resting repolarization time included cases)

Thus the consecutive studied cases consisted of 108 men 92 women. The characterization of the chest pain complied by the HIP questionnaire and other relevant parameters shown in Table 1.

It can be seen from the table that the mean age as expected—was higher in cases with angina pectoris as compared with cases of non anginal chest pain (and significant so for men $p < 0.01$) also SBP was higher in the same case (and significantly so for women $p < 0.05$). It is interesting to note the high occurrence of abnormal resting repolarization in cases with non anginal chest pain although it will not be discussed here. The most important finding however was that the probability of a middle aged person presenting with recurring chest pain to have angina pectoris is 0.38 (41 out of 108) for men and only 0.03 (3 out of 92) for women. Therefore angina pectoris is almost 12 times less frequent in women than in men of comparable age. This conclusion is in absolute contrast to the above mentioned findings (from the Framingham study).

It would be fruitful to speculate about this striking difference. The whole evidence so far has been for a clear predominance of male sex in Heberden's classical description of 19 cases of angina pectoris only three women were encountered. In seven series on the subject (published between 1893 and 1959) and reviewed by Segal, the ratio varied between 9.5 and seven men for one woman.

Burch stated that angina pectoris was more common in men than in women. Finally Friedberg mentioned a ratio of three to six men for each woman.

One might argue that in an unselected population (such as that of the Framingham study) the distribution of angina pectoris could be different from cases which consult physicians. This hypothesis is very unlikely especially in view of the very divergent proportions. On the other hand, one may question the validity of history taking. In fact, in the above mentioned study from Framingham for the purpose of explaining the striking frequency of the remission rate of angina pectoris the authors discussed the possibility of bias in the interpretation of the angina symptom complex. For the rejection of this possibility they argued that the veracity of the clinical conclusion could not be judged against laboratory evidence (including coronary arteriography) because angina pectoris is by definition the evaluation of the symptomatic only. And although this argument is sound it does not preclude us from questioning the best manner of acquiring and evaluating the historical information. Proudfit and associates commented upon the faulty first impression about the disease

mitral valve prolapse syndrome

to the Editor

In the March 1979 issue of *AMERICAN HEART JOURNAL* there appeared several interesting articles about the mitral valve prolapse syndrome. In the study by Udoshu and associates (97-303, 1979) the authors made some interesting observations regarding time relations between systolic murmur and echocardiographic mitral prolapse. Although the study was not primarily designed to evaluate the acoustic characteristics of the mitral valve prolapse syndrome, I should like to make some comments regarding these characteristics.

In typical cases the murmur associated with mitral valve prolapse is meso- to telesystolic and there is correlation with the timing of prolapse on echocardiography. On the other hand, there are cases of mitral valve prolapse where we can register only early systolic murmurs but now they do not correspond with the timing of prolapse determined by echocardiography. Of six patients with protosystolic murmur described in the article by Udoshu and colleagues, five had late systolic prolapse and one had holosystolic prolapse.

In those patients with early systolic murmur and late systolic prolapse there need not be any causal relationship between the mitral valve prolapse and the murmur. The latter may represent coincidental murmur of different genesis, for instance an innocent murmur. In such cases the mitral valve prolapse in reality is silent. Perhaps the mitral valve prolapse syndrome only rarely or never causes early systolic murmurs.

There are some practical implications of this presumption. Subjects with systolic murmur which is related to the mitral valve prolapse generally have a less favorable prognosis regarding progression of mitral regurgitation or the risk of developing infective endocarditis, when we compare them with those patients who have only an isolated systolic click. Hence in subjects with the mitral valve prolapse syndrome and protosystolic murmur with or without an associated systolic click, the mere existence of the murmur perhaps does not influence the prognosis.

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Spontaneous resumption of sinus rhythm after prolonged AF

To the Editor

In the Case Report of spontaneous resumption of sinus rhythm in an elderly patient after 13 years of permanent atrial fibrillation, Dr Chevalier (*AM HEART J* 113:361, 1979) describes a case showing an interesting and rare event. We had a similar experience with two patients (*RI Med J* 325:297, June 1977) who on recent follow-up visits, have been noted to maintain normal sinus rhythm. As noted also by Dr Chevalier, we believe that Holzmans' theory offers the best explanation for this phenomenon. We postulated the following. Atrial fibrillation is usually explained on the basis of two mechanisms—i.e. the unifocal theory and the reentry phe-

nomenon (or the circus movement). It is possible that progressive fibrotic changes taking place in the atria may abolish atrial fibrillation. In the case of unifocal theory, the triggering focus may be eradicated as it gets incorporated into the fibrotic process. In the case of the reentry phenomenon, it is possible that the fibrotic process interrupts the reentry pathway and terminates atrial fibrillation. In any case, it is necessary that the sinus node be capable of taking over once atrial fibrillation ceases. If this was not the case, sinus arrest would result on cessation of atrial fibrillation, as was seen in the case described by Rees and colleagues (*AM HEART J* 90:127-130, 1975). Thus the change from chronic atrial fibrillation to spontaneous sinus rhythm probably represents worsening of the conduction system.

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Adsorption of NTG

To the Editor

We agree with Cacace and associates that adsorption of nitroglycerin to glass containers does not create many problems; our own results concerning this item are consistent with their findings. However, the clinical importance is doubtful when you don't know how much NTG is retained in the infusion system. Therefore we conducted an infusion set adsorption study.

NTG solutions were prepared from an ethanolic stock solution containing 1% w/w of NTG by diluting with distilled water to a concentration of 5 mg/ml. The solution was filtered through an 0.2 micron filter and after discarding the first 50 ml. (we found up to 25% decrease of NTG after filtering the first portion) was filled into 5 ml. glass ampules. After sealing the ampules were heated for 30 minutes at 100°C (Branje and Berghuis).

Five milliliters NTG was added to 500 ml. of normal saline in a glass bottle and a polyvinyl chloride (pvc) infusion system was connected. Flow rate was kept constant with an Ivac 531 flow controller. Flow rates used were 0.25, 0.50, 0.75 and 1.00 ml/minute (equivalent to 12.5, 25, 37.5 and 50 micrograms per minute respectively). Samples were retained at zero, 30, 60, 90, 120, 180, 240, 300 and 360 minutes and were immediately assayed by means of the kinetic method of Yap and co-workers. At the same time samples drawn from the glass container were assayed; this concentration did not change during the experiment.

The results are summarized in Table I. The loss of NTG turns out to be flow-dependent; after a rapid decrease a gradual increase is subsequently seen which perhaps results in a plateau after six hours. For the fastest flow rate this seems to be at 90% of the original concentration whereas it is only 60% for the lowest.

Most reports concerning the use of NTG infusions don't mention the type of infusion set they use. Our results indicate that this omission is not justified. Much time is spent on determining stability of intravenous fluids in bottles or bags,

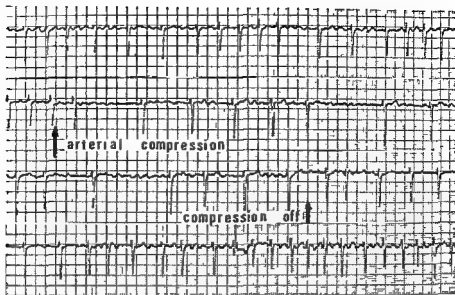


Fig 1 Continuous rhythm strip of a 45 year old woman with multiple A V fistulae in the left thigh. Upon compression of the left femoral artery the ventricular rate slows markedly from approximately 125 beats per minute to approximately 60 beats per minute with resumption of the previous rapid rate when the compression is released

additional example illustrating the great degree to which the atrioventricular node is under the control of the autonomic nervous system

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Possible association of pneumonitis with amiodarone therapy

To the Editor

Amiodarone hydrochloride (Cordarone) is an effective agent in the treatment of various arrhythmias. We would like to give a brief report on a patient with pneumonitis possibly related to the administration of this drug.

A 50 year old male who had suffered myocardial infarction and ventricular tachyarrhythmias received amiodarone 400 mg per day. One month later he started to complain of fatigue, tachypnea at rest and dyspnea on exertion. On examination there were decreased breath sounds but no wheezing or rales. The chest roentgenogram showed diffuse interstitial and intra alveolar shadows which were indistinguishable from pulmonary venous congestion (Fig 1). Despite

diuretic and digitalis therapy his condition deteriorated. Pulmonary function tests demonstrated a native defect (FVC = 195 liters, 46% of predicted value, severe impairment of gas transfer ($pO_2 = 46$ mm, $pCO_2 = 36$ mm Hg)). Hemodynamic studies excluded cor failure (CI = 3.0 L/min/M, PCWP = 2 mm Hg); demonstrated increased pulmonary arteriolar resistance (dyne sec/cm⁵) and increased pressure in the pulmonary artery (48/16 mm Hg) and right ventricle (46/0 mm Hg). In the absence of another apparent cause, an adverse reaction to amiodarone was suspected and the drug was discontinued. Prednisone 60 mg/day was started and the patient's condition improved rapidly. The chest roentgenogram at complete resolution of the infiltrates (Fig 1) and the pulmonary function tests returned to normal.

Several factors indicate that the pulmonary manifestations and clinical symptoms seen in this patient may be attributed to amiodarone. First, there was a normal base line of pulmonary functions before the administration of this drug. Second, there was a latent period between the initiation of therapy and the onset of illness. Third, amiodarone was the only drug taken by the patient. Cessation of this agent and substitution of therapy resulted in a prompt normalization of the clinical picture, radiologic changes and functional abnormalities. The chest roentgenogram and pulmonary function tests are compatible with hypersensitivity pneumonitis.

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| Parameter | Men (N = 108) | | Women (N = 92) | |
|----------------------------------|--------------------------|---------------------------------|-------------------------|---------------------------------|
| | Angina pectoris (N = 41) | Non anginal chest pain (N = 67) | Angina pectoris (N = 3) | Non-anginal chest pain (N = 89) |
| Age (mean \pm SD) | 59.44 \pm 9.20 | 50.18 \pm 9.62 | 58.50 \pm 7.00 | 54.31 \pm 9.71 |
| SBP (mean \pm SD) | 132.19 \pm 37.6 | 130.97 \pm 17.45 | 157.0 \pm 12.60 | 137.13 \pm 30.50 |
| DBP (mean \pm SD) | 82.19 \pm 21.5 | 83.50 \pm 8.44 | 88.0 \pm 4.78 | 83.75 \pm 15.40 |
| resting HR (\bar{X} \pm SD) | 69.73 \pm 11.87 | 72.69 \pm 12.67 | 69.00 \pm 13.44 | 71.82 \pm 11.93 |
| CTR (mean \pm SD) | 0.467 \pm 0.03 | 0.457 \pm 0.03 | 0.520 \pm 0.07 | 0.508 \pm 0.05 |
| Resting ST T changes (%) | 63.4 | 28.3 | 66.6 | 55.4 |

SD = standard deviation DBP = diastolic blood pressure SBP = systolic blood pressure HR = heart rate CTR = cardiothoracic ratio.

of angina pectoris, and Welch and co-workers underlined the frequent non-concordance between the history of angina pectoris in women and their findings on the coronarogram.

The superiority of the HIP questionnaire used by us compared to the more conventional one used in the Framingham study lies in the fact that it accounts for not only the positive indicators to the angina symptom complex but also for its negative indicators thus permitting a more balanced evaluation of the chest complaint in a given person. The fact that in women uncomplicated angina pectoris is much more infrequent than in men and even in these women the history of angina pectoris is an insecure predictor of coronary artery disease is corroborated also by elegant correlations with coronarographic and anatomical findings.

In conclusion in reality not only do men far outnumber women for uncomplicated angina pectoris but also the diagnosis of typical angina pectoris in a woman complainant of chest pain is, in the light of our findings, very questionable from the beginning and only a very meticulous systematic search and with cross matching history taking can secure a valid conclusion.

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Branham's sign with atrial fibrillation

To the Editor

In 1890 Branham described the transient slowing of the heart rate which occurs during manual compression of an arteriovenous fistula. We recently encountered a patient who demonstrated Branham's sign in the presence of atrial fibrillation. In surveying the literature and the many hundreds of patients described therein with arteriovenous fistula, we were unable to find a case of Branham's sign during atrial fibrillation. Our patient was a 45-year-old female with multiple arteriovenous communications in her left thigh, who had developed congestive heart failure as a result. She had a rapid irregular heart rate of 140 to 130 per minute. Upon manual compression of the femoral artery there was a dramatic and almost instantaneous slowing of the heart rate to approximately 60 beats per minute, with an immediate resumption of the rapid rate as soon as the compression was terminated (see Fig. 1).

The mechanism of the phenomenon in atrial fibrillation is undoubtedly the same as in patients with sinus rhythm, namely, a reflex response due principally to the increase in blood pressure and the decrease in venous filling. The difference lies in the fact that whereas the exquisite control of heart rate by the autonomic nervous system is usually exercised via effects upon the sinoatrial node in the patient with atrial fibrillation control is via the atrioventricular node. Branham's sign in the presence of atrial fibrillation provides an

Book reviews

Cardiovascular Review By Gerald C Timmis MD, Baltimore 1979 The Williams & Wilkins Company 227 pages Price \$10.95

This is a review of the highlights of reports that appeared in American cardiovascular journals for the past 7 years. This brief review of selected papers includes such subjects of heart diseases as ischemic heart disease, valvular heart disease, arrhythmias, conduction defects, effects of therapy and drugs, acromegaly, amyloidosis, asymmetric septal hypertrophy, athletic heart, cardiomyopathy and others. The review is remarkably thorough and extensive for a book of only 227 pages. The review, like annual reviews in other fields, is useful to many readers but unlike the annual reviews this one includes selected publications over the past 7 years. Each statement is well documented to facilitate a more extensive consideration of aspects of cardiovascular problems that might interest the reader. As with most reviews of this type, this review presents the conclusions and recommendations of the authors of publications without critical analysis of the respective studies.

Venous Thromboembolism: Prevention and Treatment Edited by John L. Madden MD and Michael Hume MD, New York 1976 Appleton-Century-Crofts Inc. 240 pages

This small, succinct book of 240 pages is concerned with an important problem involving all branches of medicine. All physicians are constantly concerned about thromboembolism in all seriously ill patients. The many contributors have reviewed the problems effectively and briefly for all physicians. The chapters include discussions of risk factors, prevention, early detection of venous thrombosis, pulmonary embolism, hemodynamic phenomena, diagnosis, use of the pneumatic venous pump and prophylaxis. Each chapter is appended with a good selection of references. The illustrations are good. This is a good and useful single source on an important clinical state. The papers were presented at a symposium in 1976 in New York City.

Hypertension: Determinants, Complications & Intervention Edited by Gaddo Onesti and Christian R. Klunt, New York 1979 Grune & Stratton Inc. 462 pages Price \$39.50

This is the Fifth Hahnemann International Symposium on Hypertension, an important and common illness of man. The many presentations are grouped into five parts: namely, determinants, complications, end organ damage, benefit and risk of intervention, and therapeutic and preventive trials and community programs. It is impossible in a brief review to consider each of the many presentations adequately. In general, the presentations are good and the discussions up to date. The book should interest internists and general practitioners. The book fails to date clearly the time of the symposium. The great number of publications and symposia on hypertension in recent years makes it unavoidable to repeat what has been said many times and therefore each adds little new to the field. Let us hope the next symposium will be limited to only what is new since this fifth one.

The Treatment of Acute Myocardial Ischemia: An Integrated Medical/Surgical Approach Edited by Lawrence H. Cohn MD, Mount Kisco, N.Y. 1979 Futura Publishing Company 230 pages Price \$23.00

This book by a surgeon of the Peter Bent Brigham Hospital along with contributors from the same hospital representing

cardiology in medicine and pathology, describes techniques employed in the management of ischemic heart disease, particularly acute myocardial infarction. The book is brief, lucid, with the emphasis being on integration of the medical and surgical specialties. The eight chapters include the pathophysiology of myocardial infarction, pathophysiology, surgical techniques and policies for emergency revascularization, management of unstable angina, acute infarction, arrhythmias, mechanical complications. The principles and practices described seem to be similar to those of other large clinics groups found elsewhere in America. This book, therefore, outlines very well the practices at the Brigham.

Histopathology of Cardiac Arrhythmias By Dr. L. R. Milan 1978 Casa Editrice Ambrosiana 299 pages

This is the second edition on histopathology of cardiac arrhythmias, an important publication in cardiology. The tendency to fail to relate the structural changes in myocardium and conduction tissues to function when managing patients with heart disease. This book reveals very well structural changes associated with heart disease. Unfortunately, the functional state is not necessarily related, explained only by anatomic changes. Nevertheless, this does indicate the possible relationships of structure to function both in health and disease. The author, a pathologist, performed an excellent service to cardiology in his study. This publication, Rossi has clearly discussed and illustrated extremely well the histology of the normal conduction system and morphologic alterations associated with cardiac disease along with disturbances in the heart beat. The photomicrographs are very good and well selected. This book should be studied by all cardiologists. It is highly recommended to pathologists and anatomists.

Heart Failure Edited by Alfred P. Fishman, New York 1979 McGraw-Hill Book Company Inc. 356 pages

This book contains the presentation on congestive heart failure held in honor of Dr. Isaac Starr of the University of Pennsylvania. There were many contributors from many parts of the USA. The presentations were concerned with basic aspects of myocardial contraction, direct assessment of cardiac contraction, indirect assessment of cardiac performance, consequences of heart failure, and therapy of heart failure. Each presentation reflects the opinions and conclusions of the authors. The papers are brief and the illustrations and text clearly presented. As is true to a great extent, the accuracy of the measurements are not critically discussed and instrumentation is prominent in the presentations. Because recordings are obtained, their usefulness is convincing in the understanding of CHF. The literature is completely represented. A reader who is interested in opinions of the various contributors to the symposium finds them clearly expressed in their respective reports.

This reviewer would like to take this opportunity to express his admiration for Dr. Isaac Starr, a fine man known for his meticulous research and dedication to medicine and scholarship. Dr. Fishman and the steering committee have done a worthy and admirable job in planning and conducting the symposium. With best wishes to Dr. Starr, an outstanding clinical investigator.

Circulatory System Dynamics Edited by Abraham Moodegraaf, New York, San Francisco and London 1978 Academic Press, Inc. 361 pages Price \$36.00



Fig 1 Posteroanterior x ray views of a 50-year old male patient. Left panel: Film taken on August 6 1978 (patient receiving amiodarone) shows diffuse interstitial and intra alveolar shadows. Right panel: Film taken on August 16 1978 after stopping amiodarone and with prednisone shows complete resolution of the infiltrates.

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Announcements

II World Congress of Cardiac Rehabilitation

The second World Congress on Cardiac Rehabilitation will be held on November 30 through December 3 1981 in Jerusalem Israel. For further information contact Secretariat II World Congress on Cardiac Rehabilitation POB 16271 Tel Aviv Israel.

ISFC International Lecture

Dr Edgar Haber Dept of Cardiology Massachusetts General Hospital, Boston will be the first International Lecturer of the International Society & Federation of Cardiology His lecture entitled "Immunological probes in cardiovascular disease" will be given at the Royal College of Physicians, London at 6 00 PM on December 4 1980 under the chairmanship of Sir Douglas Black President, Royal College of Physicians. Dr Haber will also deliver ISFC lectures in Edinburgh and Glasgow (details to be published later) All lectures are sponsored by May & Baker Ltd., Dagenham Essex, England For further information, contact Madame Marianne de Figueiredo Central Office International Society & Federation of Cardiology P O Box 117 CH 1211 Geneva 12 Switzerland. Telephone (022) 476755

IX World Congress of Cardiology

The IX World Congress of Cardiology will be held in Moscow U.S.S.R. on June 20 through 26, 1982. Further information is available from: Secretariat Organizing Committee USSR Cardiology Research Center Petrovskaya per. 10 Moscow 101837 U.S.S.R.

International Symposium on Urokinase

The second International Symposium on Urokinase will be held in Geneva Switzerland, on April 27 and 28, 1981. Under the auspices of an international scientific committee, the scientific program will include lectures on these topics: basic studies on urokinase; urokinase in ophthalmology; controlled trials in deep vein thrombosis; new aspects of urokinase therapy in pulmonary embolism; and other aspects of urokinase therapy. Deadline for receipt of abstracts is February 28, 1981. For further information, contact Professor P. M. Mancucci, Via Pace 15 20122 Milan Italy.

This is a very good review of the important procedures employed in medicine and physiology which relates the role of bioengineering to the study of normal and abnormal circulatory function. The author included reviews of the circulatory system, blood flow measurements, arteries, veins, microcirculation and the heart. Anyone seriously involved in cardiology should find the book extremely interesting. The author does not exhaust the subjects selected for his ten chapters nor does he include a careful review of the literature, but the presentations selected are important ones briefly reviewed as he considers the engineering and biophysical applications to understanding the behavior of the circulation. Even though this book is not written for practicing cardiologists, those in training in cardiology should know these selected principles of hydrodynamics and hemodynamics. This is a good small book (first volume on biophysics and bioengineering) by Noordegraaf, who has devoted much time to bioengineering.

Critical Cardiac Care, Volume V. Edited by Ephraim Donoso, M.D. and Stafford I. Cohen, M.B. New York 1979. Stratton Intercontinental Medical Book Corporation. 248 pages. Price \$98.50.

The volume of *Current Cardiovascular Topics on Critical Cardiac Care* contains 13 chapters on important acute problems in cardiology. Among the subjects discussed are acute myocardial infarction, arrhythmias, cardiogenic shock, acute left ventricular congestive heart failure, hypertensive crises,

surgical emergencies, and nursing care. This is a practical clinical publication which presents the current concepts and practices in diagnosis and management. Readers will find this book to really consist of a series of 13 separate papers, each reflecting the contributors' points of view. Students, interns, residents, and fellows in medicine and cardiology as well as general practitioners and internists would find the volume to be helpful. Surely, differences of opinion will become evident as each paper is studied. This is a good clinical book for the practicing doctor. The reader should realize that the views expressed in this publication reflect to a great extent mainly those of the authors.

Cardiology Update: Reviews for Physicians. By Elliot Rapaport, Editor in Chief. New York 1979. Elsevier Publishing Company. 364 pages. Price \$74.95.

Cardiology Update is another annual review of cardiology. This volume is well written and authentic. Some of the subjects included are echocardiography, cardiac blood pool imaging and myocardial imaging, pulmonary nuclear scanning, hemodynamic studies, cardiac pacing, role of coronary bypass surgery, aortic counterpulsation and management of hypertension. The many discussions are clearly presented. There is no doubt that it is much more effective to study the original publications. However, this book is a concise source of discussions of important aspects of cardiology. This is a good book for the busy physician.

Books received

Fundamentals of Mobile Coronary Care, second edition. By Leonard B. Rose, M.D. and Beatrice K. Rose, M.D. Baltimore 1979. The Williams & Wilkins Company. 116 pages. Price \$13.00.

Artificial Cardiac Pacing. Edited by Edward K. Chung, M.D., F.A.C.P., F.A.C.C. Baltimore 1978. The Williams & Wilkins Company. 391 pages. Price \$34.00.

Respiratory Physiology—the Essentials, second edition. By John B. West, M.D., Ph.D. Baltimore 1979. The Williams & Wilkins Company. 182 pages. Price \$11.50.

The Handbook of Critical Care Medicine. Edited by Max Harry Weil, M.D., Ph.D., and Robert J. Henning, M.D. New York 1979. Fischer Medical Publications. 205 pages.

Cardiac Valve Prostheses. By Edward A. Lefrak and Albert Starr. New York 1979. Appleton-Century-Crofts, Inc. 419 pages. Price \$24.50.

The Biochemistry of Atherosclerosis. Edited by Angelo M. Scanu, with Robert W. Wasler and Godfrey S. Getz. Associate Editors. New York 1979. Marcel Dekker, Inc. 548 pages. Price \$49.75.

now commercially available) so as to produce two rates of infusion a basal rate of 50 μ L/hr and an eightfold higher rate for mealtimes. The high rate is activated by the patient pressing a guarded button on the side of the pump; the rate automatically returning to the basal after a pre set period currently 17 minutes. The pump receives 2 or 3 ml disposable plastic syringes filled with highly purified porcine insulin (Actrapid Novo Industri Copenhagen) diluted as necessary for each patient with 0.154 mol/L saline according to insulin requirements (see below).

The pump weighs about 300 g, measures about 7 by 14 by 2 cm, and is worn by the patient on a belt around the waist or in a special shoulder harness.

Insulin is delivered from the infuser via a fine nylon cannula (Portex Ltd) which is implanted in the subcutaneous tissue of the anterior abdominal wall. This area was chosen to minimize the effects on insulin absorption known to occur when insulin is injected subcutaneously into exercising limbs. Extra fine cannulae were used to avoid discharge of insulin from the tip due to random flexing and in the hope of these cannulae being more biocompatible.

A single cannula has been used at the same site for 2 months without problems; normally they are changed every 2 to 3 weeks. Infection has not been observed at the implantation site and no tissue reaction has been felt or observed. Other workers have employed a fine metal needle attached to connecting tubing for administration and this needle is changed daily by the patient.

Infusion strategy

Control on the patient is conventional regime is used as the basis for setting the initial insulin infusion rate. The same total daily dose is generally infused on day 1 (including mealtime steps) and subsequently the dose is increased or decreased in approximately 20% steps according to the blood glucose levels achieved. The basal infusion rate was about 1.3 to 1.8 U/hr in most of our patients; other workers have quoted 12.5 to 15 mU/kg/hr. The mealtime increase is activated 30 minutes before breakfast, lunch, and the evening meal.

In a study of six patients undergoing CSII at home for prolonged periods (2 to 4 months) subjects were taught to monitor their own blood glucose with glucose oxidase reagent strips (Dextrostix) either estimating the value from the

color chart provided or reading the value in a reflectance meter. When blood glucose readings exceeded 10 mmol/L they were instructed to initiate an extra high rate infusion. When values exceeded 15 mmol/L they injected soluble insulin (Actrapid) by conventional means at a separate subcutaneous site and telephoned for advice—in case there was system malfunction or intercurrent infection, for example, Syringes were replaced by the patient daily.

Blood glucose control

We have considered that the aim of this technique is to keep blood glucose concentrations below about 10 to 11 mmol/L (180 to 200 mg/100 ml) since there is epidemiological evidence from the Bedford and Whitehall population surveys in England and from studies in the Pima Indians of Arizona that significant microvascular complications do not develop in patients with post load blood glucose values below this level.

In (fully ambulant) diabetic subjects treated by CSII on a metabolic ward for up to 4 days mean daily blood glucose levels ranged from 5.5 to 8.4 mmol/L. After initial adjustments in dose hypoglycemia did not occur as confirmed by significant reduction in the M value (an arbitrary measure of control which increases with both hyper and hypoglycemia and has extra weight for low values).

Patients who were treated at home for 2 to 3 months (maximum 111 days) had estimated mean \pm SD blood glucose levels over the entire period of between 4.8 ± 1.6 and 7.5 ± 1.6 mmol/L. Glycosylated hemoglobin assay confirmed that glycemic control was brought into the normal or borderline diabetic range.

Intermediary metabolite control

We tend to think of diabetes as a condition characterized *sine qua non* by abnormalities of glucose metabolism. Of course there are many other intermediary metabolites which are disturbed in diabetes and might equally or alone be responsible for the tissue complications. By the same score hormones such as glucagon and growth hormone are present in increased amounts or at least inappropriately high amounts for the level of glycemia. The concept of control is obviously becoming much wider particularly as our understanding of the cause of diabetic microangiopathy is so deficient.

Editorials

A new approach to improved metabolic control in diabetics Continuous subcutaneous insulin infusion

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In recent years great efforts have been placed in developing new methods of improving control in insulin dependent diabetic patients. The main incentive is the increasing realization that the late tissue complications of diabetes, particularly the microangiopathies, almost certainly depend for their evolution on the duration and severity of the metabolic disorder of diabetes.¹ If these abnormalities of metabolism could be returned towards normal it may then be possible to slow, halt or reverse the progress of retinopathy, nephropathy and neuropathy in diabetic subjects.

Unfortunately this postulate of a link between control and complications is still an article of faith rather than a reality and the major stumbling block is the difficulty or (some would say) impossibility of achieving and maintaining metabolic near normality using conventional insulin injection therapy. Clearly what is required is a prospective controlled trial between patients randomly allocated their prevalent insulin therapy (ordinary control) or a super control regime. It is to achieve the strict control of the latter type that various mechanical devices are currently being investigated.

At the outset we know that these devices must fulfil certain criteria. They should be free from

complications at the point of insulin delivery to the body; one would expect prolonged intravenous administration to be unsuitable because of the risks of thrombosis and infection. They must not restrict the physical activity of the patient; bulky bedside apparatus like the so called artificial pancreas is thus excluded. Furthermore such devices must be of low cost and applicable to most types of diabetic patients so as to enable random allocation to a fairly large trial group of patients.

Our approach has been continuous subcutaneous insulin infusion (CSII) using a dual rate portable syringe pump.² As will emerge most or all of the above requirements are met by this system. The absence of a large subcutaneous pool of depot insulin, the rapid mobilization of the small volumes delivered and the inherent flexibility of the apparatus in which the diabetic patient has control over the rate of insulin delivery commended it as a potential method of achieving long term strict control which was acceptable to the patient.

Technique

CSII is an open loop device i.e. it does not employ continuous blood glucose sensing with feedback control on insulin delivery as does the artificial pancreas³ and for this reason alone it becomes smaller, less complex, more reliable and truly portable. Our prototype delivery system was a modification of a quartz crystal controlled single rate syringe pump, the Mill Hill Infuser

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insulin withdrawal if the delivery cannula is accidentally removed from the subcutaneous or during intercurrent stress and illness blood glucose values can rise quickly and ketosis may develop. Prompt corrective action in these circumstances must be taken on the basis of frequently monitored blood glucose estimations. Until a reliable metabolic sensor is developed which will warn of loss of control outpatient use of open loop systems should probably remain a research procedure under the closest supervision.

Trends

Further miniaturization of infusers will make them more acceptable to larger numbers of diabetic patients. The sophistication of microprocessor control may in the future add great flexibility of infusion rates and offer monitoring facilities and say audible warning of pump malfunction.

The dream of an implantable insulin delivery system is still far from being realized. New methods and routes of administration of insulin need to be evaluated. CSII is but one approach. Perhaps the greatest priority is for a controlled prospective and randomly assigned trial testing the effects of prevalent and super control on microangiopathy. Only then will we be certain of the therapeutic intensity to be used toward achieving good control even with conventional treatments.

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It was encouraging that in our initial studies of patients treated by CSII for just 24 hours not only blood glucose but also blood lactate and pyruvate the ketone body 3-hydroxybutyrate and the major gluconeogenic precursor alanine were also returned towards nondiabetic concentrations. 'Tamborlane and associates' have found that plasma cholesterol triglyceride free fatty acids and branched chain amino acids are also restored to normal after 7 to 14 days of CSII.

There is no information yet on whether glucagon growth hormone and other counter regulatory hormones are normalized during subcutaneous infusion.

Insulin levels and doses

Fasting plasma free insulin concentrations during CSII are about 10 mU/L, i.e. not far removed from those of the nondiabetic subjects. Pharmacokinetic studies are beginning to indicate that the peak of circulating insulin following the mealtime step up is at about 75 minutes so that activating the prandial rate 30 minutes before a meal and allowing 45 minutes for peak glucose absorption should produce a best fit of insulin and nutrients.

It is interesting to note that work in animals indicates that about 50% of the insulin injected subcutaneously is destroyed (presumably digested by proteolytic enzymes) and so it never reaches the blood in biologically active form. This probably also applies to humans. One may speculate that the small volumes infused would suffer less enzymatic destruction and lead thereby to improved control.

Control and microvascular disease—the kidney

Radioimmunoassay of urinary albumin has demonstrated that elevated albumin excretion rates are present in some diabetic subjects even before the onset of clinical proteinuria—i.e. that detectable by reagent strips such as Albustix. This microalbuminuria seems to be mainly caused by increased glomerular capillary permeability rather than by renal tubular dysfunction. It is not known whether microalbuminuria progresses to clinical diabetic nephropathy but it must at least be taken as an index of small vessel abnormalities in diabetes.

CSII has recently been used to establish 1 to 3 days of near normoglycemia in a group of seven insulin requiring diabetic subjects of long known

duration of diabetes who were known to have increased urinary albumin excretion during conventional therapy. Even over this short period of good control microalbuminuria was reduced in all patients and was normalized in three.

These patients must presumably have structural changes in the glomerular capillaries—e.g. basement membrane thickening. So fast was the change in permeability as to suggest functional rather than structural alterations during metabolic near normalization. It follows that even in some long standing diabetic patients glomerular permeability can still be returned to normal and perhaps then nephropathy can be delayed. More work is needed in this area.

Control and microvascular disease—the eyes

Two patients treated for 3 months by CSII had at the start of therapy rapidly progressing florid diabetic retinopathy. Serial fluorescein angiograms were used to assess the response to near normoglycemia. In one patient (mean \pm SD blood glucose 5.9 ± 2.0 mmol/L) the progress of the retinopathy was halted and in the other case (mean \pm SD blood glucose 6.1 ± 2.1 mmol/L) the retinopathy markedly regressed.

Interpretations must of course be guarded in a condition known to suffer spontaneous variations in clinical course. However there seems good reason to believe that even severe retinal microangiopathy may respond to super control.

Cautions

One type of diabetic subject who may be unsuitable for CSII is the truly 'brittle' patient. We should be careful to define this condition as a rare syndrome of wide fast and unpredictable swings in blood glucose seemingly unrelated to food exercise or insulin administration. Control does not seem to be much improved in the few brittle patients we have studied. Perhaps mechanisms such as variations in subcutaneous absorption and endogenous insulin production are unchanged by this approach at least when using the present simple infusion strategy.

As in all open loop systems patients treated by CSII have little or no insulin reserve. The subcutaneous pool during infusion is small, one factor which may explain why hypoglycemia is not a big problem compared with intensified efforts at good control using conventional depot therapy. However it does mean that during absolute or relative

many significant differences from voluntary continuing smokers. This investigation established empirically that a voluntary ex smoker is on the average a different kind of person from the persistent smoker and has a lower risk of CHD regardless of smoking. Even if no such difference had been demonstrated the drawing of conclusions about causality from comparisons between voluntary ex smokers and voluntary continuing smokers would remain illegitimate. An epidemiology that sanctioned such conclusions would have no claim to be scientific.

How then can we establish cause? Several attempts have been made to circumvent the difficulties that arise from the heterogeneity within human populations and the phenomenon of self selection. The rigorously controlled intervention study referred to above has been approached by Rose and Hamilton. Male smokers were allocated randomly (a) to the intervention group which was subjected to intensive advice to give up smoking or (b) to the normal care group which received no special advice over and above that encountered in ordinary life. The "intensive advice" was successful in reducing average levels of smoking in the intervention group much more than those in the normal care group. However up to 1978 the death rate in the intervention group was 1.74 per 100 man years (based on 98 deaths) the rate in the normal care group was slightly but not significantly lower at 1.63 per 100 man years based on 94 deaths. Findings for specific causes of death were not reported but because in the general male population of comparable age deaths from diseases of the circulatory system constitute nearly 50% of the total it seems unlikely that mortality from this cause was reduced appreciably in the intervention group. These data therefore do not bolster the causal hypothesis.

Twin pairs discordant for smoking habits have great research potentiality but as the Surgeon General notes "The result has been inconclusive." The main practical difficulty for this kind of investigation is of course the limitation imposed by small numbers particularly of monozygotic (MZ) twins who tend to be highly concordant for smoking habits. In the largest survey published so far Cederlof and associates recorded only seven deaths from CHD in the pooled low group of smoking discordant MZ twins and nine in the pooled high group of present

smoker co twins. The corresponding findings for smoking discordant pairs of dizygotic (DZ) twin pairs were 12 deaths (pooled low) and 26 deaths (pooled high). This latter ratio is in line with the value expected on both causal and constitutional views. Among smoking discordant MZ twin pairs the simplest constitutional hypothesis would predict equal numbers of deaths in the low and high smoking groups whereas a pure causal theory would predict equality of ratios in series of similarly discordant MZ and DZ pairs. Neither the causal nor the constitutional theory is excluded by these small numbers. The trend favors constitutional and combined (causal plus constitutional) interpretations.

Unfortunately studies of twins remain subject to certain ambiguities even when numbers are large. If for example deaths in smoking MZ twins were found to exceed those in their non-smoking co twins we would be unable to distinguish between the causal hypothesis "smoking causes CHD" and the converse causal hypothesis "CHD or an associated condition causes the habit of smoking." Equal numbers of deaths in the two groups would favor neither of these hypotheses and would point to a constitutional interpretation.

One type of evidence that in principle could distinguish between causal and converse causal hypotheses on the one hand and constitution hypotheses on the other is that which relates secular (temporal) change. On a causal hypothesis a change in cigarette consumption should be followed by a change in mortality rate the magnitude and sign of which should be consistent with the strength of the causal connection. According to the converse causal hypothesis changes in CHD or an associated condition cause the changes in smoking. If that hypothesis holds then changes in CHD mortality rate might either precede or follow corresponding changes in smoking. If neither the causal nor the converse causal hypothesis is valid then no systematic correlation between the trends in cigarette consumption and CHD mortality rate should be observed.

In practice secular trends abound in complexities not the least of which is the inaccuracy of death certification coupled with changes in the International Classification of Diseases. Secular changes in other causal factors have also to be considered. By good fortune neither complication appears to be as serious in connection with CHD

Smoking and coronary disease

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According to Feinstein 'a licensed epidemiologist can obtain and manipulate the data in diverse ways that are sanctioned not by the delineated standards of science but by the traditional practice of epidemiologists. In this absence of delineated standards it is scarcely surprising that different investigators draw diametrically opposed conclusions. Thus we find on the one hand Shunkin proclaiming: If there is any summit of achievement in cancer research during the past several decades it must be the discovery of irrefutable proof and obvious importance of the fact that tobacco smoking causes lung cancer in man and is associated with other severe hazards to health. By contrast Oldham concludes: we still do not know how cigarettes cause lung cancer nor even if we are particularly rigorous in our use of scientific logic whether they do.

A similar confusion prevails in connection with ischemic heart disease. Perhaps the most detailed exposition of the thesis "cigarette smoking is a cause of coronary heart disease" is given in the recent report by the Surgeon General. Remarkably, the thesis rests on only two types of epidemiological evidence neither of which nor both jointly are adequate to establish cause.

Inevitably the first type of evidence concerns the positive graded association that has generally but not invariably been observed between smoking and the risk of death from ischemic heart disease. Needless to say the Surgeon General is well aware that association does not necessarily imply causation; the link could be explained

if people who were constitutionally liable to heart attacks were also constitutionally liable to smoke. (I should add that a positive association is neither a sufficient nor even a necessary condition for causation. As pointed out previously in this JOURNAL a negative genetic association between the predisposition to smoke and the predisposition to a disease could mask a weaker causal connection.)

The Surgeon General dismisses the constitutional alternative by invoking the second type of epidemiological evidence. It should be noted however that the fact that risk in smokers reverts to normal or nonsmokers' levels after they cease to smoke is contrary to the constitutional concept. Curiously the fact itself is denied by the entries in the Surgeon General's own Table 5—the risk of death from coronary heart disease (CHD) in each of the eight categories of persons who had discontinued smoking for five or more years lies between the levels in comparable current smokers and 'never smokers'.

However, the claim that this evidence is contrary to the constitutional concept is fallacious. If from a population of smokers certain individuals were selected randomly by the investigator and were successfully persuaded to give up smoking and if in all other pertinent respects they did not differ on the average from those randomly selected smokers not subjected to such persuasion and who continued to smoke, then a significant reduction of mortality in the ex-smoker group relative to that in controls would render the constitutional hypothesis improbable to an extent determined by the level of statistical significance. But a comparison of mortality rates in voluntary self-selected ex-smokers with that in voluntary self-selected continuing smokers can not discriminate between causal and constitutional hypotheses. A recent study of voluntary ex-smokers before they stopped smoking showed

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Clinicopathological study of the heart and coronary arteries of autopsied cases from the community of Hisayama during a 10-year period Part IV QS waves in the precordial leads

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Myocardial infarctions unrecognized during life were frequently found at autopsy. In the epidemiological study of coronary heart disease the scalar electrocardiogram is employed as one of the most useful tools in the diagnosis of this disease and frequently offers unequivocal objective evidence of its presence. However it is well known that abnormal Q and QS waves in the precordial leads are seen also in persons without myocardial infarction. Some of these waves are transient.

Surawicz and colleagues¹ suspected that 0.5% of the electrocardiograms examined had an absent R wave in Lead V₁. Jedlicka² reported that Q_s and QR forms were observed in Lead V₁ in 2 or 3%. However the frequency of QS waves in the precordial leads without infarction is not known in the general population.

This report concerns QS waves in the precordial leads found in persons of an autopsy series from a Japanese community Hisayama town during a ten year period and further shows the limitations of the scalar electrocardiogram in the diagnosis of myocardial infarction especially a old one.

Materials and methods

Hisayama town is a farming community adjoining Fukuoka City on Kyushu island Japan.³ The population in this community was 6 521 in 1960, 7 140 in 1965 and 7 154 in 1970 by national census. Population distribution by age and sex was not substantially different from the rest of Japan.³ The residents aged 40 years or over have participated in periodic medical examinations offered by us since the year 1961. Participation rates of the residents in the biennial examinations were approximately 90% except for one

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as might be expected. Analysis implies that the rate of smoking associates inversely with the duration of the average latent period between the initiation of the disease process and death from CHD. High levels of smoking associate with a short latent period and relatively early death while nonsmokers enjoy a long latent period and a relatively long life. If smoking causes CHD by (plausibly) shortening the latent period then because the average daily rate of smoking is much higher in young and middle aged men and women than in old persons then the latent period normally constant with age in other diseases should increase with rising age where CHD is concerned. Furthermore over the period 1921 to around 1962-7 when cigarette consumption in both sexes in England and Wales was rising the latent period should have shortened the reduction should have occurred earlier in men than in women.

None of these expectations of the causal theory is borne out by the mortality statistics. The average latent period appears to be almost constant throughout the adult range. It was also nearly constant (tending to increase if anything in middle aged women) from 1921 to 1973. Nevertheless large increases in the levels of fatal CHD were recorded but these were unaccompanied by a systematic shortening of the latent period. The simplest interpretation of the increases is that they were the consequence at least in part of earlier under recognition of the disease. The extent of under diagnosis appears to have been fairly uniform in both sexes up to about the age of 75. A constant factor of under diagnosis would not distort estimates of the duration of the latent period.

We have to consider the possibility that changes in other risk factors might have occurred so as to oppose and cancel those caused by the changes in smoking habits. This is not impossible although bearing in mind the large differences in the secular changes of smoking by

the two sexes and their marked age dependence the demands made of the hypothetical counteracting factors are formidable. Changes in diet especially the consumption of animal fats and cholesterol cannot be invoked because on a causal hypothesis they would have exacerbated the effects of smoking over a substantial part of the period 1921 to 1973.¹⁰

To the best of my knowledge the three kinds of investigation discussed here—random intervention trials, studies of smoking discordant twins and secular trends—provide the only epidemiologically based evidence that bears critically on the causal versus the constitutional alternative. The evidence available so far does not allow us to conclude that smoking causes ischemic heart disease.

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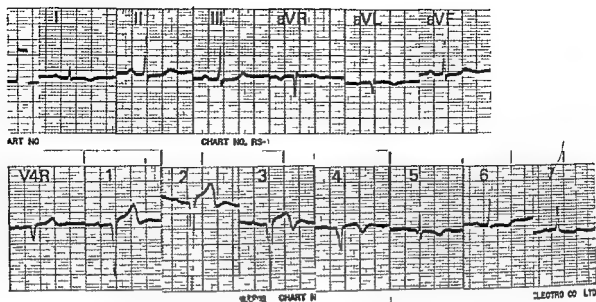


Fig 1 S A 58-year old male tracing made May 30 1963 The patient had a typical cardiac pain in October 1959 and was treated under the diagnosis of myocardial infarction This tracing shows an abnormal Q wave in Lead a_{VL} and QS waves in Leads V_1 through V_4 The T wave was inverted in Leads I a_{VL} and V_1 and was terminally inverted in Leads V_5 through V_6 Postmortem examination revealed a healed myocardial infarction involving the anteroapical and lateral walls of the left ventricle

in origin Five of these subjects showed left ventricular hypertrophy pattern by voltage criteria (RV_2 or $RV_6 + SV_1 > 35$) as well Leads in which QS waves were present are summarized in Table III Four persons showed QS waves in Leads V_{4R} and V_1 and one individual exhibited these waves in Leads V_{4R} through V_2 The other eight subjects showed an initial R wave in the leads to the right of those with QS waves A normal initial R wave in the leads farther to the right did not imply that the QS wave was pathognomonic of myocardial infarction Fig 2 reproduces the tracing of one of these individuals

Electrocardiograms of seven subjects showed QS waves in the precordial leads and a left ventricular hypertrophy pattern QS waves were present in Leads V_{4R} and V_1 or in V_{4R} through V_2 in all of these tracings In all of them QS waves were deep and the elevated ST segment showed upward concavity T waves in the right precordial leads were upright in six individuals In the other subject QS waves in the right precordial leads were accompanied by an upright T wave in one year and by an inverted T wave in another year One subject showed clockwise rotation as well

Two individuals showed complete left bundle branch block in other years Therefore QS waves in these persons may be due to incomplete left bundle branch block One of these individuals

showed left ventricular hypertrophy pattern The tracings of one case are reproduced in Fig 3

In two subjects dilatation of the right atrium was considered to be responsible for QS waves in the right precordial leads A shallow QS wave with an isoelectric ST segment was present in Lead V_1 in both of these individuals In one of them, P waves in Leads II and III were upright and sharp and a slurred r wave was present in Leads a_{VR} and V_{4R} Dilatation of the right atrium was recognized at autopsy (Fig 4) In the other subject P waves in Leads II and III were not large but dilatation of the right atrium and ventricle was found at autopsy

Electrocardiograms with precordial QS waves and clockwise rotation were recognized in five subjects QS waves were present in Lead V_{4R} and V_1 in three of them QS waves were found in Leads V_{4R} through V_1 in one year and in Leads V_{4R} through V_2 in another year in one subject In the other individual QS waves were localized in Leads V_{4R} through V_2 in one year and in Leads V_{4R} through V_2 in three other years (Fig 5) QS waves were not deep in four of the five individuals The ST segment was elevated in four of the five subjects T waves were upright in two individuals and were inverted in the other two subjects The other subject showed ST segment elevation with an inverted T wave in one year and an

year. At every periodic examination a resting electrocardiogram was taken from each participant with flat hot stylus type machines using the standard 12 leads plus Leads V_R and V_T . The recording speed was 25 mm per second. All of the electrocardiograms were read by Dr Hirota at each examination. For this study the electrocardiograms of the autopsied persons were reexamined by Drs Hirota and Hiyoshi.

All efforts were made to obtain an autopsy on all of the deceased persons in this community. The number of autopsied persons aged 40 years or over at the time of death was 339 (181 men and 158 women) during the first ten year period from Nov 1 1961 to Oct 31 1971. Distribution of these by age and sex is presented in Table I. The mean autopsy rate was approximately 84%.

Heart and coronary arteries were examined after fixation in 10% formalin. The subepicardial coronary arteries were cut transversely at 2 to 3 mm intervals and both of the ventricles were also cut transversely at 1 cm intervals from the apex to the base. Histological examination was made on one of the transverse sections containing both papillary muscles and also on the section containing suspected lesions. A zone of necrosis or scarring of 1 cm or more in the maximal dimension was called myocardial infarction. Lesions of histological age of 5 weeks or more using the criteria described by Mallory and colleagues were considered old.

Results

Electrocardiograms had been taken from 308 (161 men and 147 women) of the 339 autopsied persons at least once during the periodic examinations. QS waves in the precordial leads were recognized in 46 persons (21 men and 25 women). Excluding WPW syndrome and complete bundle branch block none of the features of the electrocardiogram other than QS and abnormal Q waves was considered in the selection of cases. Distribution of individuals by the number of tracings displaying precordial QS waves is presented in Table II.

There were nine individuals exhibiting old myocardial infarction (antroseptal six antroseptolateral one circumferential two). QS waves were limited to the Lead V_R through V_2 in two V_R through V_3 in four and V_R through V in three. In all of them QS waves were accompanied by ST segment elevation excluding Lead V_R . QS waves

Table I Age and sex distribution of autopsied persons by 10 year age groups

| Sex | Age groups (years) | | | | | | Total |
|-------|--------------------|-------|-------|-------|-------|-------|-------|
| | 40-49 | 50-59 | 60-69 | 70-79 | 80-89 | 90-99 | |
| Men | 13 | 20 | 54 | 64 | 23 | 7 | 181 |
| Women | 11 | 18 | 28 | 55 | 41 | 11 | 158 |
| Total | 24 | 38 | 82 | 119 | 64 | 18 | 339 |

Table II Distribution of individuals by number of tracings with QS waves in one or more precordial leads from V_R to V_6 *

| Sex | Number of tracings | | | | | | Total |
|-------|--------------------|----|---|---|---|---|-------|
| | 1 | 2 | 3 | 4 | 5 | 6 | |
| Men | 10 | 4 | 2 | 2 | 1 | 1 | 20 |
| Women | 7 | 11 | 3 | 1 | 0 | 4 | 26 |
| Total | 17 | 15 | 5 | 3 | 1 | 5 | 46 |

*Numbers from whom electrocardiograms were taken: 308 (161 men and 147 women).

were deep in all subjects. Abnormal Q wave in the lead farther to the left was found in only one of these nine individuals. In all but this one subject the Q wave was not recognized in the left precordial leads. In eight subjects the elevated ST segment showed upward concavity. In the other one the ST segment showed upward convexity but review of the history revealed no evidence suggestive of acute myocardial infarction at the time of this examination. The T wave was upright or terminally inverted in the leads with a QS wave in eight individuals. In the other subject the T wave was upright or terminally inverted in Leads V_R through V_2 and was inverted or terminally inverted in Lead V_3 , showing the QS wave. In four patients precordial QS waves were recorded at the examination in 1961. In two individuals they appeared at the third examination following symptoms suggestive of myocardial infarction. In the other three subjects they appeared in the later tracings but symptoms suggestive of myocardial infarction were not revealed by a review of the history. Fig 1 is a reproduction of the tracing of one of the infarction cases.

In 13 persons without myocardial infarction Q waves in Leads V_R , V_4 or V_5 suggested that QS waves in the right precordial leads were positional

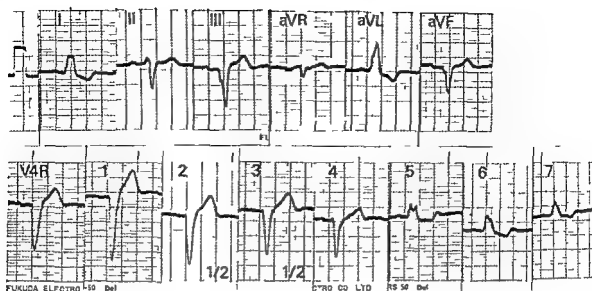


Fig 3A K. K. 79 year-old male tracing made May 6 1965 This tracing shows complete left bundle branch block



Fig 3B This tracing was taken on May 21 1966 It shows QS waves in Leads V₁ and V₂ QS waves in these leads may be due to incomplete left bundle branch block. The subject died 2 years later of pancreatic cancer Heart weight was 240 gm

cardiac infarction case can be normal in some years¹.

The most important criterion of the scalar electrocardiogram for the diagnosis of old infarction is the presence of QS and/or abnormal Q waves. However cases of QS waves in the precordial leads especially in the right precordial leads without myocardial infarction were frequently reported. An abnormal Q or QS wave in the right precordial leads was reported to be recognized in

the cases of septal infarction,¹⁶ left ventricular hypertrophy,¹⁷ right ventricular hypertrophy and dilatation,¹⁸ right atrial dilatation,¹⁹ primary myocardial disease amyloidosis,²⁰ acute ischemia of the myocardium,²¹ left bundle branch block, left anterior hemiblock,²² septal focal block, clockwise rotation, pulmonary emphysema,²³ deformity of the thorax,²⁴ allergic shock,²⁵ acute adrenal failure,²⁶ acute pancreatitis,²⁷ cerebrovascular diseases,²⁸ elec

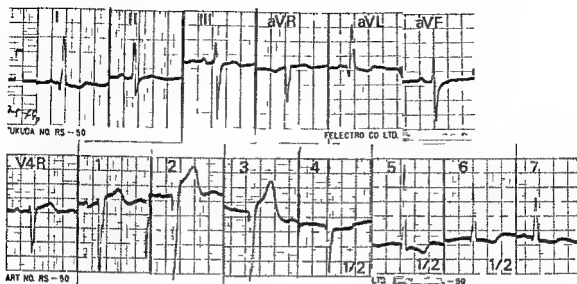


Fig 2 U K 70 year old male tracing made May 14 1962 This tracing shows a left ventricular hypertrophy pattern Lead V shows a QS wave with embryonal r wave Leads V through V show a q wave Postmortem examination revealed left ventricular hypertrophy (heart weight 510 gm)

isoelectric ST segment with an upright T wave in another year

Electrocardiograms of eight individuals showed QS waves in the right precordial leads but they were otherwise within normal limits Localization of precordial QS waves is summarized in Table IV In all of these subjects initial r waves appeared in Lead V or V₂ and increased in amplitude to an R wave in leads farther to the left QS waves of six subjects were small Autopsy revealed slight to severe pulmonary emphysema in five individuals subdural hematoma in one liver cirrhosis in one and acute intoxication with insecticide in one subject In one individual having pulmonary emphysema left ventricular hypertrophy (heart weight 335 gm) was recognized at autopsy

Electrocardiograms with precordial QS waves were tabulated by the localization of a QS wave and the presence or absence of myocardial infarction (Table V) The categories for the localization are not mutually exclusive This table indicates that QS waves localized to only one Lead—V₁ or V₂—were frequently not due to myocardial infarction All of the electrocardiograms with a QS wave in one Lead (V₁ or V₂) or in leads V₁ and V₂ had a q wave in the left ventricular leads Therefore these QS waves were considered to be positional Even if an initial r wave was present in leads farther to the right these electrocardiograms should not always be interpreted as being

due to myocardial infarction solely on the basis of QS waves Electrocardiograms with QS waves in Leads V₁ and V₂ should also be carefully interpreted

QS waves with an embryonal r wave were found in six subjects All of them had an embryonal r wave on the descending limb of the QS wave In two of them myocardial infarction was recognized at autopsy All of the subjects with myocardial infarction had deep QS waves but persons without infarction also frequently showed deep QS waves Development of the precordial QS waves in the second third or later tracing was found in both groups with and without myocardial infarction

Discussion

Electrocardiogram shows age trends⁸ sex differences⁹ and racial differences Constitutional differences also induce electrocardiographic differences The electrocardiogram is not sensitive to coronary atherosclerosis^{8,10,11} Myocardial infarction develops in only a small number of the cases of coronary atherosclerosis

The clinical diagnosis of myocardial infarction without electrocardiographic evidence has been shown to be inaccurate However it is well known that there are difficulties in the diagnosis of myocardial infarction by scalar electrocardiogram Rigid criteria will improve specificity but will reduce sensitivity The tracings of the myo

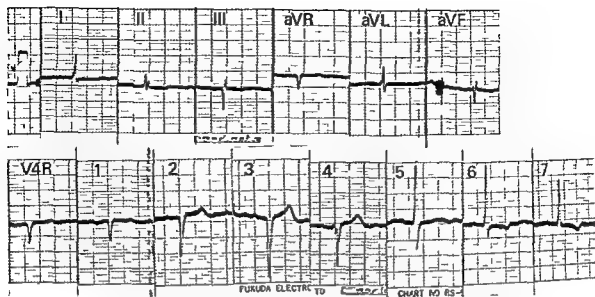


Fig 1 F T 83 year old female tracing made May 21 1962 This tracing shows QS waves in Leads V₁ through V₄ and clockwise rotation The subject died of hemorrhagic brain infarction in December 1962 Heart weight was 280 gm

Table IV Individuals with precordial QS waves without other electrocardiographic abnormalities

| Leads with QS wave | Men | Women | Total |
|---|-----|-------|-------|
| V ₁ and V ₂ | 2 | 4 | 6 |
| V ₁ through V ₄ | 0 | 1 | 1 |
| V ₁ and V ₂ in one year and V ₃ through V ₄ in another year | 1 | 0 | 1 |

trophy In clockwise rotation the interventricular septum rotates and the right septal surface faces anteriorly or even slightly toward the left and therefore the septal vector seems to be directed toward the left Myers and co workers¹⁴ maintained that in left ventricular hypertrophy cardiac rotation brought the right atrium beneath the sternum and tilted the mitral orifice to the right and forward and that in such a position left ventricular cavity potential could be recorded in Leads V₁ and V₂ Surawicz and associates¹ were of the opinion that in left ventricular hypertrophy the initial vector forces were directed downward which caused the initial negative deflection of the QRS complex in Leads V₁ and V₂ and that the tracings recorded from the position below the standard level of V₃ and V₄ showed an initial R wave

Epstein and Wasserburger⁸ reported a case of pulmonary emphysema where QS waves in Leads V₁ through V₄ were attributed to the low level of

Table V Distribution of individuals by localization of QS wave and by presence or absence of myocardial infarction

| Localization of QS wave | Myocardial infarction | | | |
|---------------------------------------|-----------------------|-------|-----|-------|
| | + | | - | |
| | Men | Women | Men | Women |
| V ₁ through V ₂ | 3 | 0 | 0 | 0 |
| V ₁ through V ₄ | 3 | 3 | 1 | 1 |
| V ₁ and V ₂ | 1 | 2 | 6 | 5 |
| V ₁ and V ₃ | 0 | 0 | 1 | 1 |
| V ₂ | 0 | 0 | 1 | 0 |
| V ₃ | 1 | 0 | 4 | 3 |
| V ₄ | 0 | 1 | 9 | 15 |

*The categories for the localization are not mutually exclusive.

the diaphragm In this case tracings taken from the position two intercostal space below the standard level were normal Some of our cases suggested that absence of the initial R wave in the precordial leads resulted from a transitional zone effect Absence of the initial R wave in the right precordial leads can theoretically occur either because of a change of heart position with relation to the electrode or because of a change of the electrode position with relation to the heart¹

From the foregoing it would appear that the diagnosis of myocardial infarction must never rest solely upon a single tracing The electrocardiographic findings should be evaluated in the light of the clinical findings and the history The

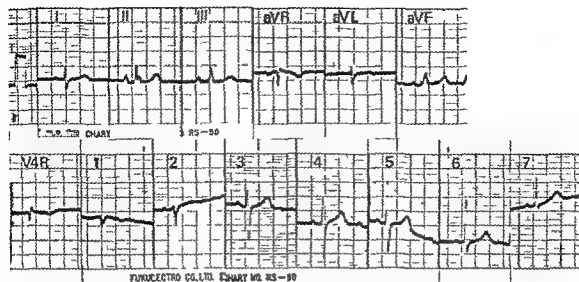


Fig 4 h. M. 80-year old male tracing made May 28 1963 P waves in Leads II and III were upright and sharp II waves in Leads aVR and V₁ were small but slurred A QS wave was present in Lead V Autopsy revealed a patent foramen ovale accompanied by dilatation of the right atrium and a dilated and thickened pulmonary artery

trolyte imbalance¹ normal heart WPW syndrome² etc

Our cases did not suffer from acute adrenal failure acute pancreatitis acute cerebrovascular diseases asthmatic attack or angina pectoris at the time of examination

Infarction in the left half of the interventricular septum can produce a QS wave in the right precordial leads and disappearance of a q wave in the left ventricular leads These changes are attributed to disappearance of the left to right septal vector The presence of a normal initial r wave in Lead V_{1R} indicates that a QS pattern in Leads V₁ and V₂ is the result of infarction and not a normal variant and the abnormal Q waves demonstrated in leads farther to the left constitute indirect evidence that the QS complexes in Leads V₁ and V₂ are also the results of infarction¹⁴ Myers and associates¹⁵ reported that a smooth QS wave in Leads V₁ and V₂ might occur as a normal variant but that a Q wave followed by a small R wave or R wave equivalent and then by a deep S wave was representative of septal infarction Our cases however suggest that the notched QS wave in the right precordial leads are not pathognomonic of septal infarction The ST segment and T wave are also changed in the acute stage of infarction The level of the ST-T junction and the contour of the ST segment is of little or no aid after healing¹

Transitory appearances of the QS wave or

Table III Localization of QS waves in the precordial leads

| Leads with QS wave | Men | Women | Total |
|---|-----|-------|-------|
| V ₁ and V ₂ | 1 | 3 | 4 |
| V ₁ through V ₂ | 0 | 1 | 1 |
| V ₁ | 1 | 0 | 1 |
| V ₂ | 1 | 1 | 2 |
| V ₁ or V ₂ from year to year | 1 | 0 | 1 |
| V ₁ through V ₂ V ₁ through V ₂ V ₁ and V ₂ or V ₁ from year to year | 0 | 1 | 1 |
| V ₁ or V ₂ and V ₃ from year to year | 1 | 0 | 1 |
| V ₁ and V ₂ or V ₃ from year to year | 1 | 0 | 1 |
| V ₁ and V ₂ or V ₃ from year to year | 0 | 1 | 1 |

abnormal Q wave in tachycardia¹ angina pectoris¹⁶ or acute pancreatitis¹⁷ were considered due to acute ischemia of the myocardium DePasquale and colleagues¹⁸ reported that local electrolyte disturbance could cause abnormal Q and QS waves Hazat and Chiche¹⁹ reported that a transient abnormal Q wave appeared more frequently in the precordial leads than in Leads II III and aVR In left anterior hemiblock the initial vector is directed inferiorly and a Q or QS wave is recorded in the right precordial leads In left bundle branch block the initial R wave may be absent in the right precordial leads because the normal depolarization of the septum is disturbed Incomplete left bundle branch block is frequently associated with left ventricular hyper-

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electrocardiogram may also be better interpreted on the basis of pattern reading in the mass population survey for coronary heart disease. Persons displaying precordial QS and abnormal Q waves in the standard electrocardiogram should be evaluated by further examination including tracings taken from the lower levels. Minnesota Code 1.1¹ seems to have some difficulties in the diagnosis of myocardial infarction. Blackburn and colleagues¹ stated that false positive labels of infarction on the basis of Q and QS criteria would be reduced in the final tabulation by excluding subjects with chronic pulmonary disease. The false positive diagnosis of myocardial infarction by QS waves in the right precordial leads would be further reduced by excluding persons with q waves in the left precordial leads.

As the accuracy of a diagnostic test is influenced by the prevalence of the disease of interest in the population studied, the precordial QS waves may have a higher diagnostic value in the population with higher prevalence of coronary heart disease.

Summary

During a ten year period from November 1 1961 to October 31 1971 339 residents aged 40 years or over at death were nonselectively autopsied in a Japanese community. Hiayama town (mean autopsy rate 84%). One or more standard 12 lead ECGs plus V₁ and V₆ electrocardiograms taken at periodic medical examinations were available for 308 of them. In 46 persons QS waves were localized in one or more leads from V₁ to V₆. By transverse sectioning of the hearts old myocardial infarction extending into the interventricular septum was found in nine of these 46 persons. Frequency of myocardial infarction cases in each category for QS localization was as follows: Lead V₁ to V₄, three of three; Leads V₁ to V₆, six of nine; Leads V₁ and V₆, three of 15; Leads V₁ and V₆, none of two; Lead V₁ none of one; Lead V₁, one of eight; and Lead V₆ one of 25.

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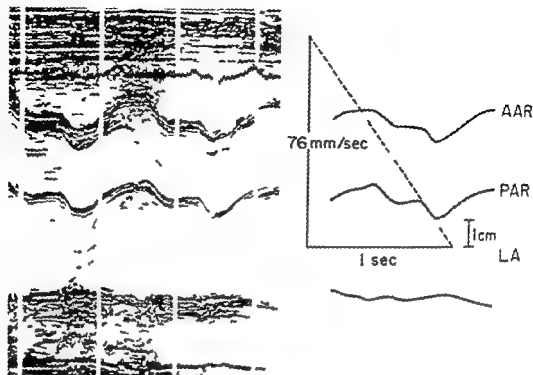


Fig 1 Schematic representation of the method used to calculate the aortic root slope AAR = anterior root PAR = posterior aortic root LA = left atrium

Table 1

| | HR (bts / min) | PR (msec) | LA/BSA (mm / M) | TAE (mm) | Ao slope (mm / sec) | LV | | LV thickness | | AVL E to F slope (mm./ sec) |
|----------------------|----------------------|--------------|---------------------|-------------|------------------------------|-------------|-------------|--------------|------------|---|
| | | | | | | ESD (mm) | EDD (mm) | IVS (mm) | PW (mm) | |
| Group 1 (No = 25) | 616 ± 16 | 1685 ± 54 | 185 ± 05 | 109 ± 06 | 580 ± 19 | 304 ± 10 | 487 ± 08 | 95 ± 02 | 99 ± 02 | 997 ± 60 |
| Group 2 (No = 15) | 736 ± 96 | 1565 ± 59 | 209 ± 06 | 76 ± 06 | 506 ± 46 | 299 ± 30 | 505 ± 31 | 154 ± 11 | 138 ± 05 | 666 ± 54 |
| P | < 0.001 | NS | < 0.01 | < 0.001 | NS | NS | NS | < 0.001 | < 0.001 | < 0.001 |

Abbreviations HR = heart rate PR = PR interval LA = left atrial echo dimension BSA = body surface area TAE = total diastolic excursion of the posterior wall of the aortic root Ao slope = slope of the posterior motion of the aortic root during atrial contraction LV = left ventricular ESD = echocardiographic end systolic dimension EDD = end-diastolic dimension IVS = interventricular septum PW = posterior wall AML = anterior leaflet of the mitral valve

All values are expressed as the mean ± standard error of the mean

the ECG were determined over a minimum of three consecutive beats (average number of beats analyzed was 4.9 per patient) and the mean was obtained (Fig 1). In all patients the aortic slope always appeared constant during atrial emptying. Beat to beat variation was small and each individual value in a given patient was within 10% of the mean for that patient. The reproducibility of this measurement determined from serial tracings was excellent and intraobserver variation was less

than 5%. The total posterior aortic root excursion in a cardiac cycle and left atrial size were also measured in standard fashion. Other echocardiographic parameters measured included the E to F slope of the anterior mitral valve leaflet diastolic and systolic left ventricular internal dimensions and the thickness of the septal and posterior left ventricular walls. All echocardiograms were recorded on Irex machines utilizing an Aerotech 2.25 MHz transducer.

Hemodynamic correlates of late diastolic posterior motion of the aortic root

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Aortic root motion on m mode echocardiography is influenced by left atrial volume change. Analysis of this motion reveals that in diastole there is both an early and late diastolic posterior motion separated at slow heart rates by a period of little motion in mid diastole. This early diastolic motion has been quantified by an atrial emptying index which is the fractional change in diastolic motion of the posterior aortic root in the first one third of diastole.¹ This index is abnormal in mitral stenosis and inversely correlated to the degree of stenosis. However in addition to left atrial emptying across the open mitral valve atrial volume change during this period should reflect left atrial filling from pulmonary venous flow.² Late diastolic posterior motion of the aortic root occurs as a consequence of left atrial contraction. During atrial systole however little or no left atrial filling occurs and ignoring the possibility of pulmonary venous reflux left atrial volume change should reflect late diastolic events in the left ventricle. In this paper we have examined the hemodynamic determinants of late diastolic posterior motion of the aortic root following the P wave of the ECG in normal individuals and

patients with left ventricular hypertrophy in whom altered patterns of left ventricular filling commonly occur.

Materials and methods

Standard m mode echocardiography was performed on 25 individuals (Group 1) including 21 consecutive normal volunteers and four patients with atypical chest pain with normal coronary arteries and left ventricular function and on 15 patients (Group 2) with left ventricular hypertrophy (IVS or PW > 11 mm) secondary to aortic stenosis hypertension or idiopathic hypertrophic subaortic stenosis. In addition the echocardiograms of 10 patients (Group 3) with a clinical diagnosis of mitral stenosis who were in normal sinus rhythm were reviewed. Patients were included only if high quality echocardiograms of the aortic root and left ventricle could be obtained. Patients with left ventricular asynergy significant coronary artery disease or more than mild aortic or mitral regurgitation were excluded. The aortic root was recorded at 50 mm/sec in a sweep from the anterior mitral valve leaflet at the level of the aortic valve. The gain was diminished until a single strong echo could be reflected from each side of the aortic root. Echocardiograms of the aortic root were rejected when several echoes were reflected from both sides of the aortic root or if the anterior and posterior aortic roots were not moving parallel in late diastole. The slope and excursion of the late diastolic posterior motion of the posterior aortic root following the P wave on

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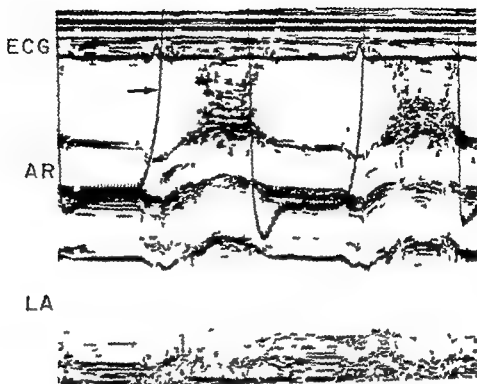


Fig 3 Representative echocardiogram of the aortic root in a patient from Group 2. The arrow is pointing to the LV pressure trace. ECG = electrocardiogram. AR = aortic root. LA = left atrium.

ic and hemodynamic data were available the aortic root slope was correlated with various left atrial and left ventricular parameters. Echocardiographic and hemodynamic data from the 16 patients studied at the time of catheterization are given in Table II. A significant inverse linear correlation was found between the aortic slope and EDCS ($r = -0.74$, $P < 0.01$) as seen in Fig 5. Because of scatter in the data we did not attempt in the individual patient to predict chamber stiffness from the value of the aortic root slope. There was no relationship between aortic slope and either left atrial size, total aortic excursion, pre-A wave pressure, A wave height, the atrial contribution to LV filling (ΔD), end diastolic dimension of the left ventricle, LV wall thickness, or left ventricular end diastolic pressure.

Discussion

The aortic root and left atrium are easily visualized with M-mode echocardiography. Although excursion of the aortic root has been related to stroke volume, Strunk and co-workers were the first to demonstrate that movement of the posterior aortic root during early diastole reflects left atrial volume change. Presumably this is related to the relative immobility of the left atrial wall except anteriorly where it comes into

contact with the ascending aorta. Furthermore, Strunk and associates devised an atrial emptying index which measured the rate of emptying of the left atrium in early diastole. This index is decreased in the presence of mitral stenosis and also in patients with increased pulmonary capillary wedge pressures and no mitral stenosis. The determinants of late diastolic motion of the aortic root have not been previously characterized. In sinus rhythm, late diastolic posterior motion of the aortic root is directly related to left atrial contraction, and in patients with complete heart block it can be shown to follow the P wave of the electrocardiogram occurring anywhere in ventricular diastole. It also disappears in the presence of atrial fibrillation. We found the slope of late diastolic posterior motion correlated best with a modulus of late diastolic chamber stiffness of the left ventricle but not with the atrial contribution to left ventricular filling or the change in left ventricular pressure following atrial contraction. A possible explanation for this association is contained in the appendix.

During atrial systole, the rate of left atrial volume change (ignoring pulmonary venous reflux) equals the rate of left ventricular volume change as there is no left atrial filling during this period. Although the aortic root slope represents

Sixteen patients the four with atypical chest pain in Group 1 and 12 patients in Group 2 in whom high quality echocardiograms of the aortic root and left ventricle could be obtained during diagnostic catheterization were further evaluated with invasive studies. Informed consent was obtained in each patient prior to study. Either before injection of any contrast agent or at least 20 minutes following completion of catheterization when heart rate and left ventricular end diastolic pressure had returned to baseline a No. 8 Millar catheter was externally calibrated and inserted via the brachial artery into the left ventricle. As the aortic root slope represents a late diastolic event it was compared with pressure and dimension measurements of the left ventricle in late diastole only. Simultaneous pressure and echo dimensions of the left ventricle were obtained before the A wave of the left ventricular pressure trace and at the A wave peak if present (12 patients) or at end diastole (four patients) at a paper speed of 100 mm/second. Chamber stiffness in late diastole (EDCS) was determined as $\Delta P/\Delta D$ and divided by the average pressure (\bar{P}). This assumes an exponential pressure dimension relationship in late diastole ($\Delta P/\Delta D = K\bar{P}$) even though this curve may be slightly altered by viscous forces occurring at the time of atrial systole.³ McLaurin and colleagues and recently our laboratory have validated the use of dimension in place of volume in determining EDCS. At least three consecutive beats were averaged and analyzed with the aid of a Graf pen, sonic digitizer and PDP 11/70 computer. The calculation of stiffness using this methodology has been previously described. All aortic root slopes were calculated at the same heart rate and left ventricular pressure as the other echocardiographic and hemodynamic parameters and were analyzed independently of the hemodynamic data.

Statistical analyses were performed using the two tailed t test for difference in means. Least squares linear regression analyses was performed and r values were calculated. All results are expressed as the mean \pm standard error of the mean.

Results

Basic echocardiographic data from Groups 1 and 2 are contained in Table I. Patients in Group 2 were significantly older, had larger left atrial

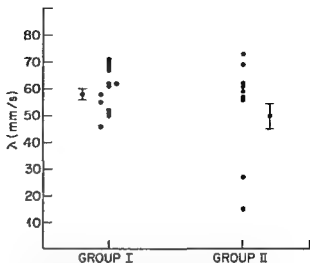


Fig. 2 Illustration showing the individual aortic root slopes (λ) for all patients in Groups 1 and 2. The mean \pm SEM for both groups is also shown. There was no statistically significant difference between the mean aortic root slopes in the two groups.

sizes, faster heart rates, thicker interventricular septums and posterior walls, and slower E to F slopes of the mitral valve than in Group 1 patients (all with $P < 0.05$). The total aortic root excursion was significantly greater in Group 1. PR intervals were similar between the two groups. The individual aortic root slopes for Groups 1 and 2 are seen in Fig. 2. The mean slope of Group 1 was slightly greater than Group 2, although this was not statistically significant. A representative aortic root echocardiogram from a patient in Group 2 with a slow aortic root slope is shown in Fig. 3. In both groups there was no correlation between either age or heart rate and aortic root slope. Patients with mitral stenosis (Group 3) had significantly slower aortic root slopes (28.8 ± 4.5 mm/sec) than in Group 1 or Group 2 ($P < 0.001$). Left atrial sizes in Group 3 (29 ± 1.3 mm/M²) were significantly greater than left atrial sizes in Group 1 or Group 2 ($P < 0.01$). A representative echo of a patient with mitral stenosis is seen in Fig. 4. As catheterization data were not available for most of the patients with mitral stenosis, no attempt was made to correlate the aortic slope with the degree of stenosis.

Although the mean slope in Groups 1 and 2 were similar, a wide range of values was present in Group 2 (15 to 73 mm/sec). Therefore, in the 16 patients in whom simultaneous echocardiographic

Table II

| No | Age | Sex | HR (bts / min) | PR (msec) | LA/BSA (mm./M) | TAE (mm) | Ao slope (mm / sec) | ESD (mm.) | EDD (mm) | LV thickness | | E to F Slope (mm./sec) |
|----------|-----|-----|----------------------|--------------|-------------------|-------------|------------------------------|--------------|-------------|--------------|------------|------------------------------|
| | | | | | | | | | | LVS (mm.) | PW (mm) | |
| Group II | | | | | | | | | | | | |
| 1 | 46 | M | 80 | 160 | 18 | 10 | 62 | 31 | 50 | 14 | 15 | 70 |
| 2 | 42 | M | 55 | 166 | 21 | 10 | 61 | 33 | 50 | 21 | 16 | 41 |
| 3 | 50 | M | 76 | 144 | 19 | 9 | 40 | 30 | 58 | 13 | 14 | — |
| 4 | 60 | F | 79 | 153 | 21 | 7 | 56 | 21 | 47 | 13 | 13 | 39 |
| 5 | 31 | M | 68 | 138 | 20 | 12 | 66 | 31 | 50 | 12 | 11 | 108 |
| 6 | 58 | F | 83 | 175 | 24 | 6 | 57 | 30 | 47 | 19 | 14 | 71 |
| 7 | 50 | M | 58 | 120 | 22 | 9 | 43 | 10 | 42 | 12 | 11 | 51 |
| 8 | 58 | F | 83 | 200 | 23 | 5 | 23 | 27 | 48 | 16 | 16 | 14 |
| 9 | 46 | M | 74 | 172 | 22 | 6 | 69 | 29 | 49 | 20 | 16 | 88 |
| 10 | 41 | M | 68 | 200 | 16 | 6 | 46 | 40 | 53 | 19 | 17 | 86 |
| 11 | 21 | M | 83 | 138 | 19 | 7 | 59 | 24 | 43 | 16 | 19 | 78 |
| 12 | 56 | M | 61 | 134 | 20 | 9 | 73 | 23 | 41 | 19 | 11 | — |
| Group I | | | | | | | | | | | | |
| 13 | 50 | M | 57 | 121 | 23 | 10 | 52 | 20 | 46 | 10 | 11 | 120 |
| 14 | 42 | F | 61 | 152 | 16 | 7 | 50 | 25 | 42 | 10 | 11 | 0 |
| 15 | 40 | M | 62 | 172 | 12 | 10 | 46 | 39 | 56 | 11 | 10 | 150 |
| 16 | 50 | F | 60 | 192 | 18 | 12 | 62 | 24 | 48 | 10 | 10 | 80 |

JP = "A" wave height in millimeters of mercury which is the numerator of the stiffness equation $P = \text{denominator of stiffness equation which is the average pressure during diastole}$ EDCS = late diastolic chamber stiffness which is equal to $\frac{JP}{\Delta D}$ where ΔD is the change in the echocardiographic internal dimension.

left atrial dimensions encountered in our patients. Therefore, as there may be a linear relationship between atrial dimensions and left atrial angiographic volumes in the range of left atrial dimensions measured, a change in dimension of the left atrium would be proportional to a change in volume. The aortic root slope as a measure of left atrial volume change would then be independent of left atrial size per se and normalization for left atrial size would not be indicated.

It is possible that the differences in slopes found in our patients were primarily related to differences in left atrial contractility. On the other hand, as we found no relationship between the aortic slope and either left atrial size or the posterior aortic root excursion, or A wave height differences in the force of left atrial contraction seem unlikely to explain all our findings. However, it is likely that in patients in Group 1 and Group 2 with similar aortic slopes, the higher left ventricular pressures in Group 2 imply a more forceful left atrial contraction as a compensatory mechanism for maintaining equal rates of left atrial emptying.

Although we ignored pulmonary venous reflux, ultrasonic flow transducers implanted in the pulmonary veins of dogs have shown a brief

retrograde pulse during left atrial contraction. Utilizing Doppler techniques, retrograde flow in the jugular vein has been demonstrated in patients with abnormal right ventricular compliance and large right atrial A waves.¹ However, even if pulmonary venous reflux is great in patients with large A waves in their left ventricular tracings, many of these same patients have increased forward flow into the ventricle from a large atrial contribution to filling. In these patients, pulmonary venous reflux may be of little importance in determining the aortic root slope.

In conclusion, we have studied the hemodynamic correlates of late diastolic motion of the aortic root. The slope of this line is decreased in mitral stenosis and in the absence of mitral stenosis may be related to diastolic properties of the left ventricle. This parameter is easily determined and with future work could become a potentially useful noninvasive index of late diastolic events in the left ventricle.

Summary

Motion of the posterior aortic root on echocardiography is related to left atrial volume change. Early diastolic posterior motion of the aortic root

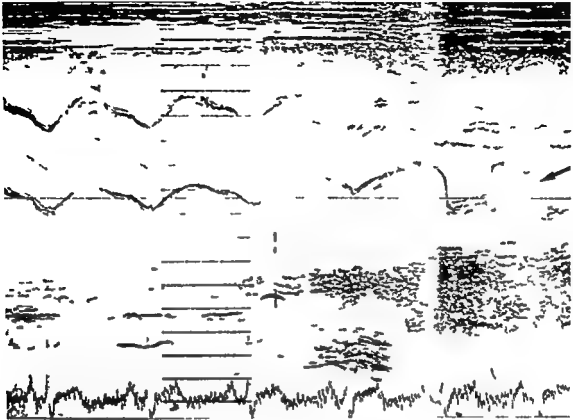


Fig 4 Representative echocardiogram of the aortic root and anterior mitral valve leaflet (arrow) from a patient in Group 3

a rate of left atrial dimension change ($\Delta D/\Delta T$ LA) and not a volume change it seems apparent that this slope should be governed by the filling characteristics of the left ventricular chamber. In turn left ventricular diastolic filling is dependent on the chamber stiffness over that portion of the pressure volume or pressure dimension curve measured. It would be most informative to have varied left ventricular pressure by changing loading conditions while measuring chamber stiffness and the aortic root slope to see if a change in slope might accurately predict a change in late diastolic chamber stiffness.

There was a good relationship between stiffness and the aortic root slope in the series of patients studied. However, because of scatter in the data we did not attempt to predict stiffness in the individual patient. This suggests that the aortic root slope might also be dependent on other variables not measured—e.g., left atrial size, left atrial contractility, and pulmonary venous reflux. In this study we did not normalize the aortic root slope for left atrial size, since the relationship between left atrial dimension and left atrial vol-

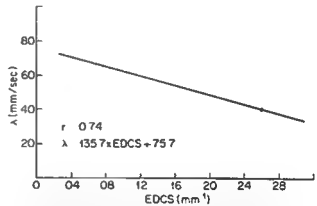


Fig 5 Graph showing the correlation between the aortic root slope (A) from the 16 patients studied invasively versus end-diastolic chamber stiffness (EDCS)

ume has not been clearly defined. In children Yabek and co-workers¹ found that left atrial echo dimensions and left atrial volumes were related by the equation $y = 8.1x^3$. Although this equation is exponential, on review of their data from Table I it could also be fit by a straight line with an r value of 0.89 over the same range of

Appendix

- 1 During atrial systole

$$\frac{\Delta V}{\Delta T}(\text{LA}) = \frac{\Delta V}{\Delta T}(\text{LV})$$

If there is no left atrial filling during atrial systole and ignoring pulmonary venous reflux

- 2 $\frac{\Delta D}{\Delta T}(\text{LA}) \propto \frac{\Delta V}{\Delta T}(\text{LA})$

If there is a linear relation between atrial dimension and volume"

- 3 $\frac{\Delta P}{\Delta V}(\text{LV}) = K\bar{P}$ or $\Delta V = \frac{\Delta P}{K\bar{P}}$

If an exponential relationship exists between P and V during diastole in the left ventricle

- 4 Substituting for ΔV in equation 1 the expression $\frac{\Delta P}{K\bar{P}}$

$$\text{then } \frac{\Delta D}{\Delta T}(\text{LA}) \propto \frac{\Delta V}{\Delta T}(\text{LA}) = \frac{1}{K} \times \frac{\Delta P}{\bar{P}} \times \frac{1}{\Delta T}$$

Therefore $\frac{\Delta D}{\Delta T}(\text{LA})$, which is the aortic root slope is inversely related to

K We found no relationship between the aortic slope and either \bar{P} or ΔP This is probably related to the fact that in this series of patients

$\frac{\Delta P}{\bar{P}}$ remained relatively constant with a wide range of pressure

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| Ejection fraction by echo | Pre "A" wave pressure (mm Hg) | ΔP (mm Hg) | \bar{P} (mm Hg) | $\Delta P/\bar{P}$ | EDCS (mm) |
|---------------------------|-------------------------------|--------------------|-------------------|--------------------|-----------|
| 0.67 | 14.3 | 16.7 | 22.7 | 0.74 | 0.15 |
| 0.69 | 13.5 | 8.6 | 17.8 | 0.48 | 0.16 |
| 0.69 | 25.0 | 27.7 | 36.4 | 0.62 | 0.26 |
| 0.86 | 4.6 | 2.8 | 6.0 | 0.47 | 0.06 |
| 0.73 | 15.5 | 7.3 | 19.2 | 0.38 | 0.09 |
| 0.66 | 23.0 | 14.3 | 30.2 | 0.47 | 0.10 |
| 0.91 | 16.7 | 11.5 | 27.5 | 0.51 | 0.21 |
| 0.81 | 19.8 | 11.5 | 25.6 | 0.45 | 0.24 |
| 0.70 | 7.4 | 6.7 | 19.8 | 0.62 | 0.10 |
| 0.49 | 18.5 | 13.7 | 25.4 | 0.54 | 0.30 |
| 0.74 | 13.7 | 6.3 | 16.9 | 0.37 | 0.14 |
| 0.81 | 14.2 | 7.6 | 18.0 | 0.42 | 0.09 |
| 0.87 | 5.0 | 8.0 | 9.0 | 0.89 | 0.14 |
| 0.42 | 5.5 | 5.0 | 8.0 | 0.62 | 0.22 |
| 0.56 | 9.0 | 6.3 | 12.2 | 0.52 | 0.16 |
| 0.81 | 6.1 | 6.1 | 9.2 | 0.67 | 0.13 |

reflects both LA emptying and filling and has been measured as the atrial emptying index. To study late diastolic motion of the aortic root we measured the slope of posterior motion of the aortic root after left atrial systole (following the P wave of the ECG) in 20 subjects without heart disease (Group 1) in 15 patients with left ventricular hypertrophy due to pressure overload (Group 2) and in 10 patients (Group 3) with mitral stenosis. The aortic root slope measured (mean \pm SEM) 58.0 ± 1.9 mm/sec in Group 1, 50.6 ± 4.5 mm/sec in Group 2 (NS vs 1) and 28.8 ± 4.5 mm/sec in Group 3 ($p < 0.01$ vs 1 or 2).

In 16 patients (four in Group 1 and 12 in Group 2) studied at catheterization an inverse correlation ($r = -0.74$, $p < 0.01$) was found between the aortic root slope (over a range of 30 to 73 mm/sec) and left ventricular late diastolic chamber stiffness measured with simultaneous left ventricular echo and high fidelity pressure recordings. No correlation was found between this slope and either left atrial size, total aortic root excursion, left ventricular pressure pre-A wave height of

the A wave end diastolic pressure or the atrial contribution to left ventricular filling. Therefore the aortic root slope in late diastole is decreased in mitral stenosis and in the absence of mitral stenosis it appears to be related to late diastolic properties of the left ventricle.

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(For Appendix see next page)

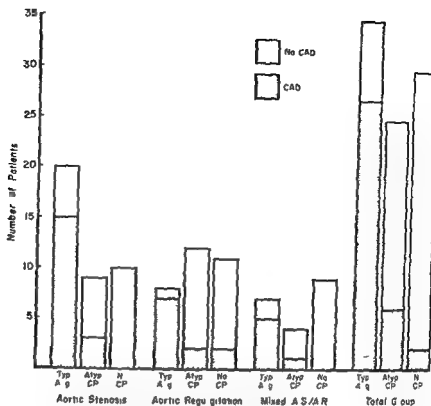


Fig 1 The correlation of angina pectoris and coronary artery disease (CAD) in patients with aortic stenosis (AS), aortic regurgitation (AR) and mixed aortic stenosis and aortic regurgitation (AS/AR). Typ Ang - typical angina pectoris, Atyp CP - atypical chest pain, No CP - no chest pain

The degree of aortic regurgitation was assessed by root aortography in the left anterior oblique projection.¹⁷ Aortic regurgitation was graded as trivial (1+) mild (2+) moderate (3+), and severe (4+). Trivial regurgitation was defined as a small amount of dye entering the left ventricle during diastole and washing out during systole and severe regurgitation was assumed when good opacification of the left ventricle was seen during the first diastole with the dye remaining in the left ventricle for several beats.

The pressures were recorded with a fluid filled manometric system the zero reference point being the mid chest level pressures were recorded on an Electronics for Medicine photographic recorder. The aortic valve pressure gradients were measured by recording simultaneous left ventricular and aortic pressures with a double lumen catheter or with two separate catheters. The left ventricle was entered retrogradely through the aortic valve or via the transeptal route.

Typical angina pectoris was defined as chest discomfort lasting for 1 to 15 minutes precipitated by effort or emotion exposure to cold or at rest which was promptly relieved by rest or nitrates.

Atypical chest pain was defined as prolonged chest discomfort lasting sometimes for hours and usually occurring at rest and not relieved by nitrates.

The aortic valve area was calculated by means of the Gorlins formula.¹⁸

On the basis of the predominant aortic valve lesion the patients were divided into three subgroups: (1) patients with severe aortic stenosis (with a valve area equal to or less than 0.53 cm²/M with mild or no associated aortic regurgitation) (2) patients with predominant aortic regurgitation (moderate to severe aortic regurgitation with no pressure gradient or with less than 20 mm Hg peak gradient across the aortic valve) and (3) patients with mixed aortic valve disease (systolic pressure gradient of equal or greater than 20 mm Hg with moderate or severe aortic regurgitation).

Statistical analysis was performed by the chi square method and by the Student's t test.

Results

There was a total of 90 patients for our final analysis. Sixty patients (66%) had chest pain of

Angina pectoris and coronary artery disease in patients with severe aortic valvular disease

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Angina pectoris is a common symptom of both aortic valve disease and coronary artery disease.¹⁻⁴ In both conditions the angina is due to an imbalance between oxygen supply and demand. The presence of significant coronary artery disease in patients with aortic valve disease is of predictive value for the operative mortality rate during aortic valve replacement. A recent report indicated that patients with aortic valve disease associated with coronary artery disease undergoing aortic valve replacement and concomitant coronary bypass surgery had better short and long term prognoses than did patients who had only aortic valve replacement and no bypass for their coronary artery disease. Therefore when we consider the possibility of aortic valve surgery it is important to know whether there is associated coronary artery disease. There is however a significant controversy in the reported prevalence of angina pectoris or associated coronary artery disease in patients with aortic valve disease.⁵⁻¹¹ The purpose of this study is to review our experience as to the prevalence of angina pectoris and associated coronary artery disease in a group of 90 patients 40 years of age and older with significant aortic valve disease who were studied in our cardiac catheterization laboratory.

Materials and methods

The records of all patients with cardiac catheterization diagnoses of aortic valve disease were reviewed. Only patients over 40 years of age were included in our study. Patients who had more than trivial mitral insufficiency, mitral stenosis, or who had had previous coronary or valve surgery were excluded. Ninety consecutive patients were finally selected for the study. All patients had complete right and left heart catheterization, left ventriculography, aortography, and coronary arteriography. Left ventriculograms were performed in a 30 degree right anterior oblique projection with 45 to 50 ml of 76% meglumine diatrizoate (Renografin). Aortograms were performed in the left anterior oblique projection and coronary arteriography was performed in multiple left and right anterior oblique projections with the Sones and the Judkins technique. Coronary arteriography is routinely performed in our institution in all adult patients with aortic valvular disease.

The cine films were recorded with a 35 mm camera at 30 seconds and were reviewed by at least two angiographers. We calculated the left ventricular volumes using the right anterior oblique projection left ventriculograms.¹² Cardiac output was determined by the dye dilution technique and by the Fick method. The ejection fraction was calculated as angiographic stroke volume divided by the end-diastolic volume. The regurgitant fraction was calculated as the fraction of the total angiographic cardiac output minus the forward cardiac output divided by the total angiographic cardiac output.

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Table I Clinical hemodynamic, and angiographic data in 90 patients with severe aortic valve disease

| | Pts with AS | | Pts with AR | | Pts with AS AR | |
|----------------------------|----------------------|-------------------------|----------------------|-------------------------|---------------------|-------------------------|
| | With CAD (n = 18) | Without CAD (n = 21) | With CAD (n = 11) | Without CAD (n = 20) | With CAD (n = 6) | Without CAD (n = 14) |
| Age (years) | 65 ± 10.1 | 60 ± 7.8 | 55.5 ± 7.4 | 54.0 ± 8.7 | 67 ± 7.3 | 57 ± 12.4 |
| Chest pain | | | | | | |
| Typical angina | 15 (83%) | 5 (24%) | 7 (64%) | 1 (5%) | 0 (83%) | 2 (14%) |
| Atypical chest pain | 3 (17%) | 6 (38%) | 2 (18%) | 10 (50%) | 1 (17%) | 3 (22%) |
| Coronary risk factors | | | | | | |
| None | 2 (11%) | 4 (19%) | 2 (18%) | 4 (20%) | 1 (17%) | 1 (50%) |
| One or more | 16 (89%) | 17 (81%) | 9 (82%) | 16 (80%) | 0 (83%) | 7 (50%) |
| Dyspnea on exertion | | | | | | |
| NYHA I II | 10 (56%) | 10 (48%) | 3 (27%) | 9 (45%) | 1 (17%) | 3 (21%) |
| NYHA III IV | 4 (22%) | 4 (19%) | 6 (30%) | 4 (66%) | 6 (43%) | 6 (43%) |
| Syncope | 5 (28%) | 8 (38%) | 0 | 6 (30%) | 0 | 3 (21%) |
| MI by ECG | 2 (11%) | 2 (10%) | 3 (27%) | 0 | 1 (17%) | 0 |
| Calcified aortic valve | 16 (89%) | 19 (90%) | 4 (36%) | 5 (25%) | 4 (67%) | 10 (71%) |
| Mean gradient (mm Hg) | 57 ± 24 | 75 ± 23 | 35 ± 5.3 | 31 ± 7.4 | 65 ± 23.8 | 67 ± 9.4 |
| AVA cm ² /M | 0.35 ± 0.11 | 0.28 ± 0.07 | — | — | — | — |
| LVEDP (mm Hg) | 18.5 ± 10.5 | 18 ± 8.1 | 27 ± 13.8 | 19 ± 10 | 34 ± 10.3 | 22 ± 13 |
| CI (L/min/M ²) | 2.4 ± 0.61 | 2.4 ± 0.4 | 2.5 ± 0.4 | 2.7 ± 0.6 | 2.1 ± 0.6 | 2.4 ± 0.4 |
| LVEF | 0.60 ± 0.12 | 0.63 ± 0.23 | 0.52 ± 0.06 | 0.57 ± 0.11 | 0.5 ± 0.13 | 0.57 ± 0.19 |
| Coronary artery disease | | | | | | |
| 1VD | 4 (22%) | 0 | 4 (36%) | 0 | 2 (33%) | 0 |
| 2VD | 8 (44%) | 0 | 7 (64%) | 0 | 3 (50%) | 0 |
| 3VD | 3 (17%) | 0 | 0 | 0 | 1 (17%) | 0 |
| LM | 3 (17%) | 0 | 0 | 0 | 0 | 0 |

Risk factors include history of hypertension diabetes mellitus smoking hyperlipidemia and family history of coronary artery disease. Abbreviations AS = aortic stenosis AR = aortic regurgitation CAD = coronary artery disease AVA = aortic valve area LVEDP = left ventricular end-diastolic pressure CI = cardiac index LVEF = left ventricular ejection fraction ± = one standard deviation IVD = one vessel disease 2VD = two-vessel disease 3VD = three vessel disease LM = left main coronary artery disease NYHA = New York Heart Association classification (Classes I-IV) MI = myocardial infarction ECG = electrocardiogram n = number of patients

27 ± 0.6 L/min/M in the coronary artery disease and non coronary artery disease subgroups respectively. The left ventricular ejection fraction was 52 ± 6% and 57 ± 11% for the coronary artery and non coronary artery disease subgroups respectively.

Patients with mixed aortic stenosis and aortic regurgitation. There were 20 patients in this group: 14 men and six women. There were six patients (30%) with associated coronary artery disease (mean age 67 ± 7.3 years) and 14 patients (70%) without associated coronary artery disease (mean age 57 ± 12.4 years). Of the six patients with coronary artery disease, two had one vessel disease, three had two vessel disease, and one had three vessel disease (Table I). In the subgroup with associated coronary artery disease, all patients had chest pain (five typical angina and one atypical chest pain). Five patients (83%) had one or more risk factors for coronary artery

disease, and four patients had dyspnea on exertion (New York Heart Association Class III or IV). None of the patients had syncope.

There was electrocardiographic evidence of myocardial infarction in one patient. In the subgroup without associated coronary artery disease, five patients (36%) had chest pain (two typical angina and three atypical chest pain). Seven patients (50%) had one or more risk factors for coronary artery disease. Six patients (43%) had dyspnea on exertion (New York Heart Association Class III or IV), three patients (21%) had syncope, and none had electrocardiographic evidence of myocardial infarction.

On fluoroscopic examination, calcification of the aortic valve was seen in 67% and 71% in the subgroups with and without coronary artery disease, respectively. The hemodynamic data are shown in Table I. In the subgroup with coronary artery disease, the mean systolic pressure gra-

these 35 had angina pectoris (39%) and 25 had atypical chest pain (Fig 1) while only 35 of the 90 patients (39%) had associated coronary artery disease. Thirty three of the 35 patients (94%) with coronary artery disease had chest pain (typical angina in 27 and atypical chest pain in six). Two patients with coronary artery disease did not have chest pain. One of these patients had 55 to 60% narrowing of the left anterior descending coronary artery; the history of the other patient was difficult to obtain because of language difficulty and his chest discomfort could not be evaluated properly. Of the remaining 55 patients without coronary artery disease 27 (49%) had chest pain (eight typical angina and 19 atypical chest pain).

The detailed clinical hemodynamic and angiographic data for all groups of patients are summarized in Table I. Each of the three groups was further subdivided into two subgroups: patients with coronary artery disease and those without.

Patients with predominant aortic stenosis. There were 39 patients in this group: 26 men and 13 women. Their ages ranged from 43 to 79 years (mean 65 ± 10 years). Associated significant coronary artery disease was present in 18 patients (46%); one vessel was involved in four patients, two vessels were involved in eight patients, three vessels were involved in three patients, and the left main coronary artery was involved in three patients. The remaining 21 patients had no associated coronary artery disease. All the 18 patients with associated coronary artery disease had chest pain (typical angina 15, atypical chest pain three). Of the 21 patients without associated coronary artery disease 11 patients (52%) had chest pain (typical angina five, atypical chest pain six).

One or more risk factors for coronary artery disease were present in 16 of the 18 patients (89%) with associated coronary artery disease and in 17 of the 21 patients (81%) without coronary artery disease. The risk factors were hypertension, diabetes mellitus, smoking, hyperlipidemia, and a family history of coronary artery disease under the age of 60. Dyspnea on exertion was present in 14 patients (78%) with coronary artery disease and 14 patients (67%) without coronary artery disease. Syncope was present in five (28%) and eight patients (38%) with and without coronary artery disease respectively.

Electrocardiographic evidence of myocardial

infarction was present in two patients in each subgroup. Calcification of the aortic valve was present in 16 patients (89%) with coronary artery disease and 19 patients without. The average mean aortic valve pressure gradient was 57 ± 24 mm Hg in the coronary disease subgroup and 75 ± 23 mm Hg for the subgroup without coronary artery disease. The average aortic valve area was 0.35 ± 0.11 cm²/M² for the coronary artery disease and 0.28 ± 0.07 cm²/M² for the noncoronary artery disease subgroups. The remainder of the hemodynamics are shown in Table I.

Patients with predominant aortic regurgitation. There were 21 patients in this group: 23 men and eight women. Eleven patients (35.5%) had associated coronary artery disease and 20 patients (64.5%) did not. The ages of patients in the coronary artery disease subgroup ranged from 43 to 76 years (mean age 55.5 ± 7.4 years) and in the non coronary artery disease subgroup ages ranged from 46 to 71 years (mean age 54.5 ± 8.7 years). One vessel disease was present in four patients (36%) and two vessel disease was present in seven patients (64%). No patient had three vessel disease. Chest pain was present in nine patients (typical angina seven, atypical chest pain two) and in 11 patients (typical angina one and atypical chest pain 10) in the coronary artery disease and noncoronary artery disease subgroups respectively.

Risk factors for coronary artery disease were present in nine patients (82%) in the coronary artery disease subgroup and in 16 patients (80%) in the non coronary artery disease subgroup.

Exertional dyspnea was present in four patients (36%) with coronary artery disease and in 15 patients (75%) without. Syncope did not occur in any of the patients with coronary artery disease but it did occur in six patients (30%) without coronary artery disease.

Calcification of the aortic valve was present in four patients (36%) in the coronary artery disease subgroup and in five patients (25%) in the non coronary artery disease subgroup. There were no significant differences in the mean pressure gradient across the aortic valve in the coronary artery and non coronary artery disease subgroups. The end-diastolic pressure of the left ventricle was 27 ± 13.8 mm Hg in the coronary artery disease subgroup and 19 ± 10 mm Hg in the non coronary artery disease subgroup. The cardiac index was 2.5 ± 0.4 L/min/M² and

artery disease. The group with aortic regurgitation had one or two vessel disease. This may explain why 83% of the patients with aortic stenosis had typical angina in contrast to 64% of patients with aortic regurgitation. Although Linhart and colleagues¹⁴ suggested that patients with aortic regurgitation may be less prone to develop coronary artery disease, the less extensive disease in the patients with aortic regurgitation in our group may in part be explained by the fact that the patients were almost 10 years younger than patients with aortic stenosis (mean age aortic stenosis 65 ± 10 years vs aortic regurgitation 55.5 ± 7.4 years). It is of interest also to note that one vessel disease was present in 29% of the 35 patients with aortic valve disease in contrast to 21% with one vessel disease of all the patients with coronary artery disease referred for coronary arteriography in our laboratory.

Similar findings of a low incidence of multivessel disease were reported by Graboyes and Cohn.¹⁵ The prevalence of coronary artery disease in our patients with typical angina pectoris was 77% in contrast to patients with atypical chest pain with only a 25% rate of coronary artery disease ($P = 0.001$). These findings agree with those of Paquay and associates¹⁶ who reported that in patients with aortic valve disease the more typical the angina the more likely these patients are to have coronary artery disease. Hancock,⁴ in the most recent report of his experience with a large series of patients with aortic stenosis commented on the significance of angina associated with dyspnea. He reported that angina occurring on exertion in the absence of dyspnea or occurring at rest with emotional stress after meals or during sleep was associated with coronary artery disease in 80% of instances whereas angina occurring only in association with dyspnea on exertion was associated with coronary artery disease in 45% of instances.

An important group of aortic valve disease patients are those with coronary artery disease who did not have angina pectoris. Only two (6.6%) of our 30 patients without chest pain had coronary artery disease. The reported incidence of coronary artery disease in the absence of angina pectoris varies widely. Graboyes and Cohn¹⁵ found 4% of patients with aortic valve disease to have associated coronary artery disease in the absence of angina pectoris. Similarly Paquay and co-workers¹⁶ found coronary artery disease in one of

19 patients (5%) and Bonchek and colleagues¹⁷ found no coronary artery disease among 4 patients with aortic valve disease in the absence of angina pectoris. Harris and associates² and Thompson and co-workers¹⁸ reported an incidence of 10% and 13% (respectively) of coronary artery disease in patients with aortic valve disease in the absence of angina pectoris. Hancock's⁴ suggestion that patients with aortic valve disease and coronary artery disease in the absence of angina pectoris may present with symptoms of heart failure. This type of patient may be similar to those with ischemic cardiomyopathy in the absence of aortic valve disease as described by Burch and associates.¹⁹ The hemodynamics in the three groups of patients are shown in Table I.

The mean pressure gradient across the aortic valve in patients with aortic stenosis tended to be lower in patients who also had coronary artery disease. There were no significant differences in left ventricular end diastolic pressure in the three groups of patients with aortic stenosis and coronary artery disease or no coronary artery disease. However, in the groups with aortic regurgitation and mixed aortic stenosis/aortic regurgitation, left ventricular end diastolic pressure was high in the subgroups of patients with associated coronary artery disease. There were no significant differences in the cardiac index between the different groups of patients.

Comparing the ejection fraction in patients with coronary artery disease in the different groups we found significantly higher ejection fractions in patients with aortic stenosis rather than in patients with aortic regurgitation ($P = 0.001$) or mixed aortic stenosis/aortic regurgitation ($P = 0.05$). There was no significant difference in ejection fraction between the aortic regurgitation group and the mixed aortic stenosis/aortic regurgitation group. There was also no significant difference in the ejection fraction between the patients without coronary artery disease and the different groups.

Calcification of the aortic valve was much more common in the groups with aortic stenosis and mixed aortic stenosis/aortic regurgitation. Dyspnea on exertion (Class III or IV New York Heart Association) was much more common in patients with mixed aortic stenosis/aortic regurgitation. Syncope was present in the coronary artery disease and no coronary artery disease subgroups. Patients with aortic stenosis, however, it occurred

dent across the aortic valve was 65 ± 23.8 mm Hg the aortic valve area was 0.27 ± 0.07 cm²/M², the left ventricular end diastolic pressure was 34 ± 10.3 mm Hg the cardiac index was 2.1 ± 0.6 L/min/M² and the left ventricular ejection fraction was $50 \pm 13\%$. In the subgroup without coronary artery disease the mean systolic pressure gradient across the aortic valve was 67 ± 24 mm Hg. The left ventricular end diastolic pressure was 22 ± 13 mm Hg the cardiac index was 2.4 ± 0.4 L/min/M² and the left ventricular ejection fraction was $57 \pm 19\%$.

Discussion

Angina pectoris is a well recognized symptom of patients with significant aortic valve disease in the absence of coronary artery disease. The mechanisms responsible for angina pectoris in aortic valve disease can be explained on the basis of an imbalance between myocardial oxygen supply and demand.^{1, 10, 22} Fallen and associates demonstrated that patients with severe aortic stenosis but no demonstrable obstructive coronary artery disease have relatively fixed coronary flow response to catecholamine administration stress resulting in abnormal myocardial metabolism and ischemia. A fixed coronary flow and decreased myocardial oxygen supply result from the fixed stenotic valve orifice and the low mean aortic pressure.

Other factors that may cause decreased oxygen supply to the myocardium in patients with aortic stenosis are the prolonged ejection time which if combined with the tachycardia of exercise results in a decreased diastolic filling period, the increased left ventricular wall tension,^{1, 2} the increased left ventricular mass² and the abnormal flow patterns in the aortic root.² Increased myocardial oxygen demand may result from myocardial hypertrophy and increased wall tension due to elevated left ventricular end diastolic pressure. In patients with aortic regurgitation angina may be due to an increase in wall tension secondary to increased left ventricular volume and to the lower coronary perfusion pressure during diastole. The presence of significant coronary artery disease in patients with aortic valve disease is an additional critically important single factor causing angina pectoris.

There is wide variation in the reported prevalence of angina pectoris in patients with significant aortic valvular disease ranging from 40 to 80% for predominant aortic stenosis^{1, 5} and 3 to

30% for predominant aortic regurgitation.²⁴ Similarly the prevalence of coronary artery disease in aortic valve disease has been reported to be within a wide range between 20 and 63%.^{10, 25, 26} This wide variation in the prevalence of angina and coronary artery disease in patients with aortic valve disease may be a result of differences in the ages of the patients studied and the variable criteria used by different investigators in defining significant coronary artery stenosis. Some authors^{1, 10, 27} have used a criterion for significant stenosis: lumen narrowing of at least 70 to 75% but others^{11, 28} have used as significant lumen narrowing of $\geq 50\%$. There is general agreement that in patients without aortic valve disease a lumen narrowing of 70 to 75% is probably needed to cause reduction of coronary flow; however we agree with Hancock¹ with Linhart and colleagues⁴ and with Moraski and associates² that in patients with significant aortic valve disease a lumen narrowing of $\geq 50\%$ can cause significant hemodynamic abnormalities in the coronary circulation.

The rate of chest pain in our total group of 90 patients was 66% whereas the rate of coronary artery disease in the same group was only 39%. This indicates that chest pain is not related to coronary artery disease in more than half of the patients with aortic valve disease. However, when aortic valve disease was associated with coronary artery disease the rate of chest pain was 94%.

The higher incidence of chest pain in patients with aortic valve disease and associated coronary artery disease as compared with patients without coronary artery disease is expected since both diseases have an additive effect upon ischemia. Of the 55 patients with aortic valve disease but no associated coronary artery disease eight patients (16%) had typical angina pectoris, 19 patients (35%) had atypical chest pain and 28 patients (49%) had no chest pain.

The distribution of coronary artery disease in the three groups of patients was 46% in predominant aortic stenosis, 35% in severe aortic regurgitation and 30% in the mixed aortic stenosis/aortic regurgitation group. Although the rate of coronary artery disease in predominant aortic stenosis was higher than in the aortic regurgitation or mixed aortic stenosis/aortic regurgitation groups the difference was not statistically significant.

The group with predominant aortic stenosis had more severe disease involving multiple vessels and included three patients with left main

Site of origin of ventricular premature beats in patients with mitral valve prolapse

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Mitral valve prolapse is a common abnormality,¹ and is frequently associated with ventricular premature beats (VPB). Although malignant ventricular arrhythmia and sudden death are rare,² they have been reported³ and are a cause for concern. Many features of VPBs have been analyzed in an attempt to predict which may have malignant characteristics and a poor prognosis. The site of origin of a VPB is thought to correlate with underlying cardiac pathology and perhaps with prognosis.

This study examines the vectorcardiogram of VPBs in ten patients with mitral valve prolapse. These VCG loops were then used to postulate the site of origin and attempt to relate this with the type of prolapse and the possible etiology of the VPB.

Methods

The study population consisted of 10 patients with mitral valve prolapse diagnosed in our Echocardiographic Laboratory. There were two males and eight females with a mean age of 29.1 ± 11.1 years. All patients had a midsystolic click and a mid or late systolic murmur. Although some of the patients had atypical chest pain, none had typical clinical features or ECG evidence of coronary heart disease. Three patients had complete cardiac catheterization which confirmed the presence of mitral valve prolapse and the absence of coronary artery disease.

Echocardiograms were performed on a Unirad

100 series Echoscope. Standard scanning techniques were used.

Vectorcardiograms (VCGs) were performed on an Instruments for Cardiac Research Model VCG 1V Vectorcardiograph. This system allows the vector loop to be interrupted 400 times per second. The Frank Lead System was used for vectorcardiograms of both the normal QRS and the ventricular premature beat. All 10 patients were having unifocal ventricular premature beats. After the vector of the normal QRS was recorded, the patients were monitored through the VCG unit until a ventricular premature beat occurred. The ventricular premature beat was stored in the machine's memory and then all three vector loops were inscribed from the same ectopic beat.

Results

The direction of the mean vector of the ventricular premature beat in both the frontal and horizontal plane for all 10 patients is shown graphically in Fig 1. The rotations of the vector loops, the type of mitral valve prolapse, and the proposed site of origin of the ventricular premature beat are shown in Table I.

Fig 2 shows the standard 12 lead electrocardiogram from patient No 9. This 16 year old female presented because of palpitation and was found to have a typical midsystolic click and midsystolic murmur. The electrocardiogram shows sinus rhythm with ventricular premature beats and is otherwise within normal limits. Fig 3 shows this patient's echocardiogram demonstrating prolapse of the posterior leaflet of the mitral valve. Fig 4 shows the vectorcardiogram performed on this patient's ventricular premature beat.

Discussion

Mitral valve prolapse is a common abnormality especially in the younger population. Auscultation

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only in patients without coronary artery disease in both groups of aortic regurgitation and mixed aortic stenosis aortic regurgitation. This is a surprising finding but it should be interpreted with caution since the number of patients under analysis was small.

There was electrocardiographic evidence of myocardial infarction present in two patients with and in two patients without coronary artery disease in the group with aortic stenosis. Myocardial infarction which is rare in the absence of obstructive coronary artery disease was reported to occur in patients with aortic stenosis³ as well as in patients without aortic valve disease and in patients with hypertrophic cardiomyopathy.²

The etiology of myocardial infarction in patients with aortic stenosis but without significant atherosclerosis is unclear. The possible causes are calcific embolus, the fact that the increased cardiac mass may have been too great for the existent coronary blood supply, narrowing of the intramural coronary arteries and brief periods of hypoxia due to transient hypotension. Recently it was shown that myocardial infarction may be precipitated by coronary spasm in vessels with or without atherosclerosis.¹² There was no statistical difference in the presence of one or more risk factors for coronary artery disease in the different groups of patients.

Our study suggests that although patients with aortic valve disease and typical angina pectoris are most likely to have associated coronary artery disease, it is not possible to accurately predict this condition by clinical or hemodynamic findings. The absence of chest pain excluded associated coronary artery disease in 94% of our patients with aortic valve disease. These findings are in some agreement with the findings of several other investigators^{1,2,13} but considerably different from the findings of others^{3,14,15}. This raises the question once again whether coronary arteriography should be performed routinely in every patient with aortic valve disease undergoing evaluation with cardiac catheterization. Lanham and colleagues¹⁴ suggested that coronary arteriography should be performed in all patients undergoing evaluation for aortic valve replacement since they found significant coronary artery disease in 25% of their patients who had no angina pectoris. There is general agreement that coronary arteriography should be performed in all patients with angina pectoris when they are

evaluated for aortic valve disease. The information provided by coronary arteriography may prove to be important with regard to operative risk and long term prognosis when performing coronary bypass at the time of aortic valve surgery.³ There is however disagreement as to whether coronary arteriography should be performed in patients with aortic valve disease without angina pectoris.

Some investigators do not recommend routine coronary arteriography in patients with aortic valve disease who do not have angina pectoris.¹² This negative recommendation is based on the observation that none of their patients or those reported by others^{16,17} without angina had significant coronary artery disease. Other investigators disagree with this point of view and recommend routine coronary arteriography in all patients with aortic valve disease undergoing cardiac catheterization.^{18,19} Their reasoning is that patients with aortic valve disease who are free of angina pectoris have a definite albeit small risk of concomitant significant coronary artery disease.

Since the combination of aortic valve replacement and coronary bypass surgery seems to lower the risk of operative morbidity and mortality in aortic valve replacement and improves the long term prognosis, we agree with those who advocate routine coronary arteriography for all patients over the age of 40 even if they do not have angina pectoris. Another reason for routine coronary arteriography in patients studied for aortic valve replacement is to rule out anomalous aortic origin of coronary arteries. These anomalies occur in 0.6 to 1.2% of the total patients undergoing coronary arteriography and are more common in patients with valvular disease.²⁰ Knowing the presence of anomalous origin or the course of a coronary artery may avoid injury to the vessel during aortic valve replacement or may exclude the anomalous vessel from perfusion if this technique is used to perfuse the myocardium during extracorporeal circulation.

Summary

We studied the clinical hemodynamic and angiographic findings of 90 consecutive patients with significant symptomatic aortic valve disease 40 years of age or older to evaluate the prevalence of angina pectoris in relation to coronary artery disease and the effect upon cardiac function.

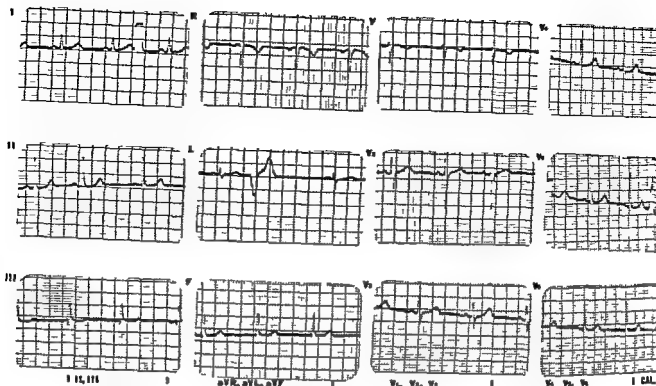


Fig 2 Standard 12 lead electrocardiogram recorded on patient No 9 The rhythm is normal sinus with an occasional ventricular premature beat The QRS morphology is within normal limits

lapse both using Holter monitoring and exercise testing. Despite this apparent cause and effect relationship Shappel and Marshall⁴ have reported two patients with sudden death and mitral valve prolapse who showed no documented arrhythmia despite extensive ECG and maximum exercise testing. Lichtman and co workers¹⁴ have noted a high prevalence of sinus bradycardia and sinus arrest and suggest that this might be one possible mechanism for sudden death.

Since most investigators do feel that there is some relationship between ventricular arrhythmia and sudden death the mechanism of ventricular irritability becomes important in planning preventive therapy. Criley and colleagues¹⁵ postulated that during systole the mitral leaflets become progressively inflated and thus are exposed to an abnormal stress as they balloon into the left atrium tugging on the chordae and papillary muscles. During early diastole the leaflets now above the level of the mitral annulus abruptly dump the blood contained within their ventricular aspect into the base of the left ventricle. This impact may produce a mechanical stimulus for producing a ventricular ectopic beat. This hypothesis however does not account for the intermittent nature of this arrhythmia. Micro

electrode studies in monkeys and dogs have found that muscle fibers situated in the mitral valve leaflet are capable of developing spontaneous diastolic depolarization resulting in automatic impulse initiation when stretched or exposed to epinephrine.^{16, 17} Muscle bundles with accompanying muscular vessels are known to exist normally in the mitral leaflet of man.¹⁸ Therefore in addition to possible mechanical stimulation of the myocardium by excessive movement of the mitral valve leaflet a functional anatomic basis for arrhythmias associated with mitral valve prolapse syndrome may be ectopic impulse initiation that occurs in the valve leaflet muscle bundles.¹⁹

At the present time antiarrhythmic therapy is suggested only when the patient is bothered by palpitations or when malignant characteristics of VPBs are noted. Therapy is usually limited to oral propranolol but may occasionally require diphenylhydantoin when a prolonged QT interval is noted. Propranolol may be the drug of choice since in addition to its intrinsic antiarrhythmic action it decreases left ventricular contractility, increases left ventricular volume and therefore may lessen myocardial ischemia resulting from excessive traction on the papillary muscle.^{20, 21}

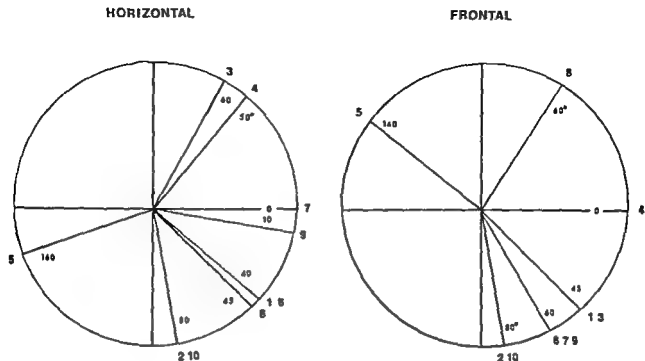


Fig 1 Graphic representation of the mean QRS vector of the ventricular premature beats in all 10 study patients. The numbers on the outer circumference identify the study patient both in the frontal and horizontal plane

Table 1

| Pt no | Age | Sex | Horizontal | | Frontal | | Prolapse | Origin of VPB |
|-------|-----|-----|------------|----------|----------|----------|-------------|-----------------|
| | | | Rotation | Mean QRS | Rotation | Mean QRS | | |
| 1 | 26 | F | CW | +40 | CW | +45 | post | LV posterobasal |
| 2 | 26 | F | CW | +80 | CW | +80 | post | LV posterobasal |
| 3 | 31 | M | CCW | -60 | CCW | +45 | post | RV anterobasal |
| 4 | 39 | F | CCW | -50 | CW | 0 | post. | RV free wall |
| 5 | 47 | F | CW | +160 | CCW | -140° | post | LV posterobasal |
| 6 | 30 | F | CCW | +40 | CCW | +60 | post | LV posterobasal |
| 7 | 27 | M | CCW | 0 | CCW | +60 | post & ant | LV posterobasal |
| 8 | 49 | F | CCW | +45 | CCW | -60 | post & ant | LV posterobasal |
| 9 | 16 | F | CCW | +10 | CW | +60 | post | LV posterobasal |
| 10 | 20 | F | CW | +80 | CW | +80 | post. & ant | LV posterobasal |

Abbreviat as CW = clockwise CCW = counterclockwise

tory and echocardiographic features of mitral prolapse may be seen in asymptomatic populations with an incidence ranging from 6.3% to nearly 18%. One of the major clinical concerns with this abnormality is the high incidence of ventricular arrhythmia and the occasional occurrence of sudden death.^{8,9}

It is thought that there is some relationship between sudden death and the previous occurrence of ventricular premature beats. Winkle and associates¹ studied seven patients with prolapse

who survived one or more episodes of life threatening ventricular arrhythmias. VPBs were present in the ECG of six of the seven and were frequent during exercise testing and Holter monitoring. Wei and colleagues⁸ described 10 patients with mitral valve prolapse among a larger group of patients with refractory ventricular arrhythmia. Four of these patients with prolapse had a history of cardiac arrest due to ventricular fibrillation. Other investigators^{1,11} have noted frequent VPBs in patients with mitral valve pro-

TRANSVERSE PLANE Σ 

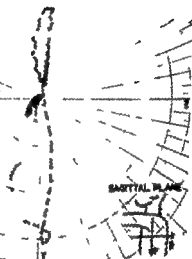
X



FRONTAL PLANE

IV

X



SAGITTAL PLANE

Fig 4 Vectorcardiogram of a ventricular premature beat recorded in patient No 9. The vector loop is interrupted 400 times per second.

superiorly in the frontal plane are thought to arise from the posterior wall of the left ventricle and those that are directed inferiorly arise from the anterior wall of the left ventricle. VPBs arising from the base of the left ventricle would have forces directed anteriorly, inferiorly, and to the left. They would be superior or inferior depending on whether the VPB arises from the posterior or anterior wall. Beats arising from the apex of the left ventricle would be directed posteriorly, superiorly, and to the right. All beats originating in the right ventricle had a left bundle pattern. The majority were directed inferiorly and to the right. Rosenbaum felt that they arose from the anterior wall of the right ventricle and not from the septum. They originate in the myocardium and not the Purkinje tissue since the inscription of the initial part of the QRS is slow. He felt that they may arise from the anterior papillary muscle of the right ventricle

and that perhaps the stretching of that structure during normal mechanical activity of the ventricle could trigger ventricular premature beats.

Using this type of classification, Hiss and colleagues⁶ evaluated VPBs in a population of healthy male subjects of various ages. They found that the number of VPBs from the right ventricle were approximately three times as great as those from the left. The incidence of VPBs from the right ventricle increased fourfold from the youngest to the oldest age group (20 to 45+ years), while the rate for those originating in the left ventricle did not change significantly.

If one accepts this type of classification for the purpose of determining origin, then the significance of this site of origin must be examined. The coronary drug project data⁷ showed an increased mortality rate in patients with VPBs following myocardial infarction. However, these investigations found that this excess risk was associated

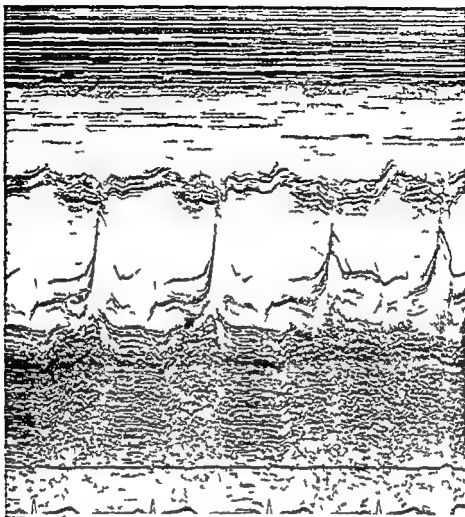


Fig 3 Echocardiogram recorded on patient No 9 The arrow indicates late systolic prolapse of the posterior leaflet of the mitral valve

radical and seldom used method of therapy is mitral valve replacement which occasionally has been thought to be necessary for the prevention of recurring life threatening arrhythmia.²¹ More recently aprindine has been used. Troup and Zipes² describe the use of this drug in seven patients with symptomatic potentially life threatening ventricular arrhythmias. Conventional antiarrhythmic drugs had been tried and were unsuccessful. Aprindine resulted in a greater than 91% reduction in the number of VPBs in 24 hours in addition to a marked reduction in the frequency and duration of ventricular tachycardia.

VPBs may be found in all age groups even in the absence of cardiac disease. Since they are so common many have attempted to find characteristics which differentiate benign from malignant

VPBs. Rosenbaum²² using electrocardiograms from humans has classified ventricular extrasystoles according to their form and their site of origin. Mautner and Girotti²³ arrived at a similar classification using pacemaker induced ventricular beats in the experimental dog. It becomes apparent from these studies that one cannot simply identify the site of origin by merely noting the presence of a classical right bundle or left bundle pattern in the frontal plane. Manning and colleagues²⁴ have noted a common discordance between the findings in the limb and the precordial leads. Because of this a determination must be made by seeing the same VPB in both the frontal and horizontal plane or by the use of the vectorcardiogram. Rosenbaum's classification²² states that VPBs from the left ventricle will have a right bundle pattern. Those that are directed

tissue judged by the slow initial forces (3) There was no relationship between the location of prolapse and the VPB morphology

Summary

This study examines the site of origin and possible etiology of ventricular premature beats (VPB) in patients with mitral valve prolapse

Ten patients with mitral valve prolapse documented by echocardiogram form the study group All patients had prolapse of the posterior leaflet and three additionally had anterior prolapse There were eight females and two males, with a mean age of 29.1 ± 11.1 years All patients were having unifocal VPBs at rest A vectorcardiogram (VCG) was taken of the VPB by a technique which allowed all VCG loops to be written from the same beat

The VCG analysis indicated that the VPB forces were directed anteriorly inferiorly and to the left in six patients In two patients the VPB was directed posteriorly inferiorly and to the left consistent with right ventricular origin One of these patients had episodes of ventricular tachycardia One was anterior superior and to the left, and one was markedly anterior superior and to the right In all patients the initial portion of the QRS was inscribed slowly The three patients with additional anterior prolapse did not show a common difference from those with isolated posterior prolapse

It is concluded that (1) The majority of these VPBs originate from the posterobasal portion of the left ventricle (2) They originate in the myocardium and not in the Purkinje tissue (3) There is no relationship between the location of prolapse and the VPB morphology

I wish to thank Ms Carol Scott for her assistance in preparing the manuscript and Dr Prem K. Gupta for performing the echocardiograms

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with frequency of VPBs but was independent of ECG criteria such as whether the VPBs originated in the right or left ventricle. Lewis and associates¹⁴ studied 165 patients with VPBs classified as either of right or left ventricular origin. Patients with no heart disease had a higher incidence of right ventricular VPBs. Of 102 patients with left ventricular disease, 51% had left ventricular VPBs. Of the six patients with right ventricular disease, five of six (83%) had right ventricular VPBs. These authors concluded that patients with right ventricular disease generally had right ventricular VPBs. In patients with left ventricular disease, the incidence of left ventricular and both right and left ventricular VPBs was much higher than in patients with right ventricular disease alone. Kennedy and Underhill¹⁵ studied 25 asymptomatic healthy patients because of frequent or complex VPBs. These beats were classified by ECG and in 10 vector criteria were also used. The beats were predominantly of right ventricular origin in 19 of 25 subjects and disappeared during exercise in 21 of 23 subjects. Three of the 10 subjects classified by vector criteria had beats which were thought to originate in the left ventricle but were still thought to be benign. Pretaras and colleagues¹⁶ studied 27 patients with chronic recurrent ventricular tachycardia. Fifteen had left ventricular tachycardia and all had organic heart disease. There were 12 with right ventricular tachycardia and they were younger, mostly female, and only three had organic heart disease. During follow-up there were three deaths and these were all in the group with left ventricular tachycardia. These authors mention that one patient had a pansystolic murmur but they do not document the diagnosis of mitral prolapse in any of these patients. It is of interest to note that one of our patients (patient No. 3) had ventricular tachycardia during an exercise test which required DC cardioversion. This patient's VPBs and his ventricular tachycardia were both consistent with right ventricular origin.

Because of this proposed relationship between the site of origin and the presence of disease, removal of disease such as left ventricular aneurysm has been suggested for recurrent ventricular tachycardia. While this may be successful,¹⁷ it is also reported that patients with right ventricular tachycardia may also improve after left ventricular aneurysmectomy.¹⁸ Tomisawa and co-workers¹⁹ described one patient with right ventricular

tachycardia which was abolished by right ventricular aneurysmectomy, and Engle and associates²⁰ describe two children with left ventricular tachycardia which was abolished by excision of a left ventricular tumor. With the exception of the rare patients with right ventricular tachycardia and left ventricular aneurysmectomy, these data are thought to validate the proposed ECG localization of ventricular tachycardia.²⁰ Bodenheimer and colleagues²¹ studied 39 patients with VPBs who had cardiac catheterization. Nineteen had left ventricular VPBs, 17 had right ventricular VPBs, and three had both left and right ventricular VPBs. Of the 19 with left ventricular VPBs, 15 had coronary disease and four were normal. Of the 17 with right ventricular VPBs, 11 had coronary disease and six were normal. The three patients with both left and right VPBs also had coronary disease. These findings indicate that in patients with chest discomfort syndrome there was no relationship between site of origin of the VPB and either the prevalence or the severity of coronary disease. These authors note that the Purkinje fibers penetrate the interventricular septum for a considerable distance from the left ventricle towards the right ventricle. Thus an impulse originating from the left ventricular portion of the septum could depolarize the right ventricle first. These authors suggested that this might explain the presence of right ventricular VPBs in three patients with isolated disease of the left anterior descending coronary artery.

We classified the origin of VPBs using vector cardiographic criteria suggested by Sano and co-workers.²² Using these criteria, it was felt that only two patients had VPBs originating in the right ventricle and the remaining eight had VPBs originating in the left ventricle. The most common site of origin was the posterobasal portion of the left ventricle. This is perhaps consistent with the hypothesis that mechanical irritation produced by the billowing valves dumping blood into the left ventricle could be the cause of this arrhythmia. A possible origin from the base of the papillary muscles seems unlikely, since that origin would have been expected to produce a superiorly oriented electrical force while ours were mostly inferiorly directed.

From this study we conclude that (1) The majority of these VPBs originate from the posterobasal portion of the left ventricle. (2) They originate in the myocardium and not the Purkinje

Cardiovascular manifestations of tricyclic antidepressant overdose

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Cardiotoxicity in tricyclic overdosage has been reported frequently during the last 15 years. Most studies¹ have focused attention on the characteristic pattern of electrocardiographic disturbances which, as Giles pointed out, is so constantly seen as to be pathognomonic. Little clinical information, however, regarding the broader aspects of the effects of tricyclic overdose upon the cardiovascular system has been accumulated.

We have recently reported on clinical findings of patients with tricyclic antidepressant (TCA) overdoses and their correlations with (TCA) plasma levels.² Our present study will concentrate only on the cardiovascular manifestations of TCA overdose. We present the results of a retrospective analysis of the cardiac manifestations of 35 cases of TCA overdosage: 23 cases with amitriptyline and 12 cases with imipramine.

Materials and methods

The clinical histories of 23 cases of amitriptyline overdose and 12 cases of imipramine overdose admitted to Yale New Haven Hospital from January 1973 to December 1978 were reviewed.

The criteria for inclusion in this study were history of tricyclic antidepressant overdose and elevated plasma levels of TCA.³ Patients who were known to have ingested significant amounts of drugs other than TCA were excluded from the study.

The patients ranged in age from 13 to 73 years; eight patients were teenagers. Twenty-seven patients were female and eight patients were male. There was no previous history of cardiac disease in any case. Twenty patients were receiving TCA drugs chronically.

The clinical protocol followed in each one of the 35 patients after admission to the intensive care unit at Yale New Haven Hospital was physical examination, routine laboratory and toxicologic determinations, electrocardiograms, and routine chest x-rays. In five patients, right-sided heart pressures and cardiac output by the modulator technique were sequentially measured through a Swan Ganz catheter placed in the pulmonary circulation using standard techniques.⁴ In addition, determination of plasma levels of TCA and their respective active metabolites were obtained. Initial blood samples for tricyclic levels were obtained within 2 to 4 hours after admission to the intensive care unit. In addition, levels were determined at variable intervals thereafter. Plasma concentrations of the parent compounds, amitriptyline and imipramine, and their respective pharmacologically active metabolites, nortriptyline and desmethylimipramine, were measured by gas liquid chromatography using a nitrogen sensitive detector accord-

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Table II Electrocardiographic manifestations of tricyclic antidepressant overdose in 35 patients

| | Number | Per cent |
|-----------------------------------|--------|----------|
| Sinus tachycardia | 25 | 71 |
| Supraventricular tachycardia | 2 | 6 |
| Premature ventricular beats | 12 | 34 |
| Prolongation of PR interval | 4 | 11 |
| Prolongation of QRS complex | 10 | 29 |
| Right bundle branch block | 8 | |
| Intraventricular conduction delay | 5 | |
| Abnormal ST segment | 10 | 28 |
| Abnormal T wave | 10 | 28 |
| Prolongation of QT interval | 30 | 86 |
| Normal electrocardiogram | 7 | 20 |

sions of normal saline solution (1.5 ± 0.7 liters) in an average of 3 hours. After fluid infusion the following hemodynamic measurements were obtained—heart rate 118 ± 12 beats per minute, pulmonary capillary wedge pressure 12 ± 3 mm Hg, mean pulmonary artery pressure 18 ± 6 mm Hg, systemic systolic blood pressure 82 ± 12 mm Hg, and cardiac output 4.8 ± 0.5 mm Hg. After fluid infusion in these five patients right-sided and left ventricular filling pressures were normalized and cardiac output was significantly increased. A small but statistically significant rise in systolic blood pressure was also observed. However, no change in heart rate was noted after the therapeutic intervention. The systemic hypotension was finally corrected in these five particular patients with the infusion of sympathomimetic amines. Of note is that the heart rate remained elevated despite complete correction of all measured hemodynamic parameters (118 ± 10 beats/minute).

Electrocardiographic manifestations on admission. Of the 35 patients with amitriptyline or imipramine overdose, sinus tachycardia was documented in 71% (25 of 35), supraventricular tachycardia was found in 6% (two of 35), premature ventricular beats were seen in 34% (12 of 35), prolongation of the PR interval (first degree A-V block) was documented in 11% (four of 35). Widening of the QRS complex was observed in 29% (10 of 35). Of these patients with a widened QRS complex, five patients had right bundle branch block and five patients had non-specific intraventricular conduction delay. Abnormal ST segments and T waves were present in 28% (10 of 35), and prolongation of the QT interval was apparent in 86% (30 of 35) (Table II). Seven of the

35 patients had completely normal electrocardiograms.

Twelve patients demonstrated severe ventricular ectopy (more than 60 PVCs per hour) in the 12-lead admission electrocardiograms. An additional patient developed severe ventricular ectopy upon arrival at the intensive care unit. Of these 13 patients, 10 patients had uniform PVCs. No patients had sustained repetitive ventricular tachyarrhythmias. Three of the original 13 patients with severe ventricular ectopy were reported as having a cardiopulmonary arrest prior to admission.

The duration of ventricular ectopic activity ranged up to 72 hours after admission, but 10 patients did not show any further ventricular ectopy after 36 hours. Intravenous infusion of lidocaine (2.0 ± 0.5 mg/minute, mean \pm SD) was used to control the frequent premature ventricular beats in all 13 patients. The use of this antiarrhythmic agent did not produce any detectable undesirable rhythm disturbances. After transfer from the intensive care unit to regular medical wards, none of these patients were found to have arrhythmias. Long-term Holter monitor tracings were obtained in all of these patients. Only one had severe ventricular ectopy (multiple premature ventricular beats) in the first Holter monitor tracing (72 hours after admission), which disappeared in the second Holter monitor recording (before discharge). Two patients had nonsevere ventricular ectopy in the first Holter monitor recording, which also disappeared at the time of discharge (second Holter monitor recording). No arrhythmias were noted in the Holter tracings of the remaining ten patients.

Evolution of abnormal electrocardiographic manifestations. Twenty-eight patients with abnormal admission electrocardiograms had the following electrocardiographic evolution during their hospital stays. Sixteen patients (including five with widened QRS complexes) had their electrocardiogram revert to normal within 72 hours after admission. The remaining 12 patients demonstrated persistent prolongation of the QT interval at 72 hours following admission.

Fig 1 presents the relationship between the duration of the QRS complex and plasma level of imipramine overdose in four patients with widened QRS complexes in which sequential TCA blood levels were available. There was a

ing to methods previously reported from our institution.¹¹

The electrocardiographic interpretations were made according to the Minnesota Code¹² for rhythm AV conduction QRS complex and ST and T waves. The QT interval was corrected for rate according to the formula of Ashman and associates.¹³ Electrocardiograms were obtained upon admission to the intensive care unit and thereafter daily until tracings were interpreted to be within normal limits. Twenty-four hour ambulatory long-term electrocardiograms (Holter monitor) were obtained in patients who had ventricular ectopy on admission at 72 to 96 hours after admission and the day before discharge from the hospital (5 to 7 days after admission). The scanning of the Holter monitor tapes was done by a highly trained physician and was reviewed by the staff cardiologist. Initially each Holter monitor tape was reviewed at fast speed (60 times real time) using a commercially available scanner. When any abnormal rhythm was identified the Holter monitor tape was replayed and the electrocardiogram was recorded in paper at a speed of 25 mm/sec. The abnormal rhythm was classified and the number of ectopic beats were manually counted. Cardiac arrhythmias were classified as supraventricular tachyarrhythmias, ventricular tachyarrhythmias, and conduction disturbances. Supraventricular tachyarrhythmias were classified as atrial premature beats (>60/hour), atrial flutter, and atrial fibrillation. Ventricular tachyarrhythmias were classed as (1) severe ventricular ectopy (either premature ventricular contractions (PVC) >60/hour, multifocal premature ventricular contractions, repetitive PVCs, or ventricular tachycardia or fibrillation) and (2) non-severe ventricular ectopy (uniform PVCs at <60/hour). Conduction disturbances were recorded as atrioventricular block and intraventricular block.

The medical treatment in this series of 35 patients with tricyclic overdose was supportive only and included intravenous fluids, sympathomimetic amines, gastric lavage, activated charcoal, magnesium citrate, and support of respiration. Hemodialysis and peritoneal dialysis were not used in these patients, and all recovered uneventfully.

Table 1 Clinical findings in 35 patients with amitriptyline (23 patients) and imipramine (12 patients) overdose

| | Number | Per cent |
|---|--------|----------|
| Tachycardia | 25 | 71 |
| Hypotension | 18 | 51 |
| Atrial gallop (S ₁) | 8 | 14 |
| Ventricular gallop (S ₃) | 4 | 11 |
| Summation gallop (S ₁ + S ₃) | 6 | 17 |
| Ejection systolic murmur | 10 | 28 |

Plasma levels The total initial plasma levels of amitriptyline plus active metabolites ranged from 180 to 1560 ng/ml with a mean \pm SD of 430 \pm 74 ng/ml, and plasma levels of imipramine plus active metabolites ranged from 150 to 1732 ng/ml with a mean \pm SD of 665 \pm 137 ng/ml.

Statistical analysis When appropriate the data were statistically analyzed by unpaired Student *t* test. A *p* value less than 0.05 was considered as statistically significant.

Results

Physical findings The admission clinical findings in the 35 patients with TCA overdose are displayed in Table 1. Tachycardia (heart rate >110 beats per minute [bpm]) was present in 71% of patients (25 of 35); hypotension (systolic blood pressure <80 mm Hg) was seen in 51% (18 of 35); hypotension occurred more often with amitriptyline overdose (65%, 15 of 23) than with imipramine overdose (16%, 2 of 12).

Cardiovascular hemodynamic measurements In five patients with marked hypotension and tachycardia a Swan Ganz catheter was placed in the pulmonary artery. Heart rate, pulmonary capillary and pulmonary artery pressures, systemic arterial pressure, and cardiac output were sequentially measured. These measurements were repeated as clinically indicated during a 24-hour period. The initial hemodynamic measurements were: heart rate 121 \pm 8 beats per minute (mean \pm SD); pulmonary capillary wedge pressure 6 \pm 3 mm Hg; mean pulmonary artery pressure 10 \pm 4 mm Hg; systemic systolic blood pressure 65 \pm 8 mm Hg; and cardiac output 2.8 \pm 1 L/min. The initial low left ventricular filling pressures (pulmonary capillary wedge pressures) were corrected with infu-

Table II Electrocardiographic manifestations of tricyclic antidepressant overdose in 35 patients

| | Number | Per cent |
|-----------------------------------|--------|----------|
| Sinus tachycardia | 25 | 71 |
| Supraventricular tachycardia | 2 | 6 |
| Premature ventricular beats | 12 | 34 |
| Prolongation of PR interval | 4 | 11 |
| Prolongation of QRS complex | 10 | 29 |
| Right bundle branch block | 5 | |
| Intraventricular conduction delay | 5 | |
| Abnormal ST segment | 10 | 28 |
| Abnormal T wave | 10 | 28 |
| Prolongation of QT interval | 30 | 86 |
| Normal electrocardiogram | 7 | 20 |

sions of normal saline solution (1.5 ± 0.7 liters) in an average of 3 hours. After fluid infusion the following hemodynamic measurements were obtained—heart rate 118 ± 12 beats per minute, pulmonary capillary wedge pressure 12 ± 3 mm Hg, mean pulmonary artery pressure 18 ± 6 mm Hg, systemic systolic blood pressure 82 ± 12 mm Hg, and cardiac output 4.8 ± 0.5 mm Hg. After fluid infusion in these five patients right-sided and left ventricular filling pressures were normalized and cardiac output was significantly increased. A small but statistically significant rise in systolic blood pressure was also observed. However, no change in heart rate was noted after the therapeutic intervention. The systemic hypotension was finally corrected in these five particular patients with the infusion of sympathomimetic amines. Of note is that the heart rate remained elevated despite complete correction of all measured hemodynamic parameters (118 ± 10 beats/minute).

Electrocardiographic manifestations on admission. Of the 35 patients with amitriptyline or imipramine overdose, sinus tachycardia was documented in 71% (25 of 35), supraventricular tachycardia was found in 6% (two of 35), premature ventricular beats were seen in 34% (12 of 35), prolongation of the PR interval (first degree A-V block) was documented in 11% (four of 35), widening of the QRS complex was observed in 29% (10 of 35). Of these patients with a widened QRS complex, five patients had right bundle branch block and five patients had non-specific intraventricular conduction delay. Abnormal ST segments and T waves were present in 28% (10 of 35) and prolongation of the QT interval was apparent in 86% (30 of 35) (Table II). Seven of the

35 patients had completely normal electrocardiograms.

Twelve patients demonstrated severe ventricular ectopy (more than 60 PVCs per hour) on the 12-lead admission electrocardiograms. An additional patient developed severe ventricular ectopy upon arrival at the intensive care unit. Of these 13 patients, 10 patients had uniform PVCs. No patients had sustained repetitive ventricular tachyarrhythmias. Three of the original 13 patients with severe ventricular ectopy were reported as having a cardiopulmonary arrest prior to admission.

The duration of ventricular ectopic activity ranged up to 72 hours after admission, but patients did not show any further ventricular ectopy after 36 hours. Intravenous infusion of lidocaine (2.0 ± 0.5 mg/minute, mean \pm SE) was used to control the frequent premature ventricular beats in all 13 patients. The use of this antiarrhythmic agent did not produce any detectable undesirable rhythm disturbances. After transfer from the intensive care unit to regular medical wards, none of these patients were found to have arrhythmias. Long-term Holter monitor tracings were obtained in all of these patients. Only one had severe ventricular ectopy (multiple premature ventricular beats) in the first Holter monitor tracing (72 hours after admission) which disappeared in the second Holter monitor recording (before discharge). Two patients had nonsevere ventricular ectopy in the first Holter monitor recording which also disappeared at the time of discharge (second Holter monitor recording). No arrhythmias were noted in the Holter tracings of the remaining 11 patients.

Evolution of abnormal electrocardiographic manifestations. Twenty-eight patients with a normal admission electrocardiogram had the following electrocardiographic evolution during their hospital stays. Sixteen patients (including five with widened QRS complexes) had the electrocardiogram revert to normal within 48 hours after admission. The remaining 12 patients demonstrated persistent prolongation of the QT interval at 72 hours following admission.

Fig 1 presents the relationship between the duration of the QRS complex and plasma level of imipramine overdose in four patients with widened QRS complexes in which sequential TCA blood levels were available. There was

progressive normalization of the QRS complex duration while the plasma levels of imipramine were falling to lower levels. The QRS complex durations were in the normal range when the plasma level of imipramine was below 200 ng/ml.

Discussion

The pharmacology of TCA on the cardiovascular system has been extensively studied.¹³ These drugs have a number of pharmacological actions that include anticholinergic activity, direct myocardial depressant activity, and a sympathomimetic activity which is related to their ability to block the reuptake of adrenergic amines. All of these actions may contribute to the adverse effects of TCA on the cardiovascular system; however, the individual dose response curves for each of these actions remains undefined. A factor further influencing TCA cardiotoxicity is that these drugs are highly concentrated by the myocardium.¹

Cardiovascular findings in TCA overdose. The most common cardiovascular signs of TCA overdose in this study were tachycardia (71%; 25 of 35 patients) and hypotension (51%; 18 of 35 patients). Previous studies^{9,10} of therapeutic and/or toxic doses of TCA have demonstrated that tachycardia is a prominent feature. This chronotropic effect could be related to several physiologic mechanisms: direct stimulation of the sinus node, reflex mechanism induced by the clinically significant hypotension, or direct effect upon the cardiorespiratory center in the central nervous system. The tachycardia observed in our patients appeared to be independent of changes in blood pressure. The five patients who were invasively instrumented demonstrated no change in heart rate when the blood pressure was restored to normal levels. This finding suggested that the tachycardia cannot be explained by a hypotension reflex mechanism alone. By this study, we were not able, however, to elucidate the operative pathophysiologic mechanism.

Hypotension was the second most prominent cardiovascular manifestation of TCA overdose, occurring in 51% of all cases. The first substantial study of TCA on blood pressure reported no change in recumbent blood pressure, but there was a significant frequency of postural hypotension. These changes were observed especially in older patients and in patients with organic cardio-

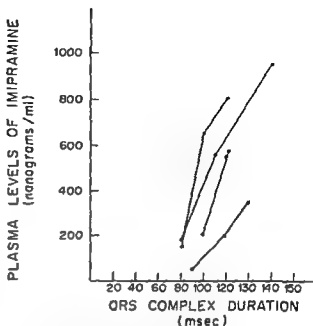


Fig. 1 Relationship between plasma levels of imipramine and duration of the QRS complex in four patients with intra-ventricular conduction defects.

vascular disease. Subsequent studies³ documented that postural hypotension is independent of age, sex, and blood levels of TCA. The mechanism whereby TCA produces hypotension is unclear,^{22,24} but it has been attributed to a peripheral effect, a myocardial depressant effect, a direct effect upon the central nervous system, and a combination of these influences.

In five hemodynamically monitored patients in our cohort with TCA overdose, hypotension was associated with marked intravascular fluid depletion, manifested by low left ventricular filling pressures and low cardiac output. When left ventricular filling pressures and cardiac output were corrected, the blood pressure increased, but it still was clinically in the hypotensive range. Hemodynamic measurement of cardiac function did not indicate left heart failure. These findings suggest a TCA-mediated afterload reduction.

Thorstrand²⁵ carefully examined cardiovascular hemodynamics in ten patients who overdosed with TCA using right heart catheterization. The hemodynamic data were obtained during and after recovery from coma. As judged by the pulmonary arterial diastolic pressure, central venous pressure, and cardiac output, myocardial failure did not occur during overdose in any of these patients.

The only other previous attempt to measure

the effects of TCA on left ventricular function in human subjects used systolic time intervals. All eight patients in that study had therapeutic levels of TCA. An increase in the ratio of pre ejection period over duration of left ventricular ejection time (PEP/LVET) was found in all patients. The authors concluded that TCA therapy is associated with a decrement in left ventricular function. In interpreting the significance of these results we note that measurements of systolic time intervals may not be adequate to evaluate left ventricular function.^{29, 31}

These two studies have produced contradictory findings on the influence of TCA on left ventricular function. The study of Taylor and Braithwaite³ using therapeutic plasma levels, suggests that these drugs depress left ventricular function. Somewhat surprisingly the study of Thorstrand using toxic plasma levels found little effect of TCA on left ventricular function. Our findings are in agreement with those of Thorstrand in that TCA at toxic plasma levels did not clinically impair left ventricular function.

Electrophysiologic manifestation of TCA overdose The electrophysiologic manifestations of TCA overdose have been reported in detail by several other investigators.³⁻³¹ In 1962 Cairncross and Gershon³² studied imipramine cardiotoxicity in anesthetized cats and dogs. These investigators were able to show that increasing doses of intravenous imipramine up to 8 mg/kg produced serious cardiac conduction disturbances which they interpreted as toxic effects on the conduction tissue. Boissier and co workers³³ in another experimental study with progressive lethal intoxication in guinea pigs mention that progressively higher degrees of atrioventricular block occurred with increasingly higher doses of TCA and that conduction impairment improved between doses (except when the point of irreversible intoxication occurred when all electrical activity of the heart ceased).

The most characteristic electrocardiographic manifestations found in patients with TCA overdose are conduction and repolarization disturbances: atrioventricular block, intraventricular conduction defects, T wave changes and prolonged QT interval. Tricyclic antidepressants exert a quinidine like action upon the conduction system in all studied species. Therefore the toxic manifestations of TCA should be similar to those induced by quinidine toxicity. Our study showed

a high incidence of conduction impairment in patients with imipramine and amitriptyline overdose: prolonged PR interval in 11%, prolonged QRS complex in 29%, and prolonged QT interval in 86%. The pathophysiologic behavior of these conduction disturbances was very similar to that reported in pigs.³⁴

Of interest is the fact that we did not document ventricular tachycardia in any of our patients, although ventricular tachycardia has been described in the preterminal phase of severe intoxications. It is possible that the bizarre wide QRS complexes which are so commonly seen in TCA overdose reflect an aberrantly conducted supraventricular tachycardia rather than ventricular tachycardia. Two of our patients, who had a supraventricular tachycardia had very wide and bizarre QRS complexes which reverted to normal when plasma levels of imipramine diminished.

It should be noted that no serious ventricular arrhythmia occurred in our patients, and only 13 patients had initial ventricular ectopic activity. These ventricular premature beats were treated in the same manner as quinidine-induced ventricular tachyarrhythmias. Since the electrophysiologic actions of both quinidine and procainamide are identical to those of TCA, it is unlikely that either drug would abolish the ventricular ectopy. They may even aggravate the electrophysiologic abnormalities because TCA induced arrhythmias may result from reentrant excitation currents secondary to slowed conduction velocity in the myocardium. Lidocaine appears to be the therapeutic drug of choice. However, abolition of ventricular activity with lidocaine may unmask serious underlying rhythm disorders which might require the placement of a temporary pacemaker. In our patients lidocaine infusion was able to control all ventricular ectopic beats without any undesirable effect. Thirteen of our patients with initial ventricular ectopy had two (24 hours each) long term Holter monitor recordings; only one patient had severe ventricular ectopy and two additional patients had nonsevere ventricular ectopy during the first electrocardiographic recording. These three patients were free of ventricular ectopy at the time of the second recording. It should be noted that no patients received antiarrhythmic drugs during that late phase of their hospitalization.

The relative lack of ventricular arrhythmias in

our cohort was surprising in view of previous reports^{13, 34, 35} which suggested a high incidence of malignant arrhythmias with TCA overdose. We found no malignant arrhythmias in any of the patients either on admission or during monitoring in the intensive care unit. Follow up Holter monitors in 13 of our patients who were felt to be at higher risk showed no ventricular or supraventricular arrhythmias during hospitalization.

Clinical implications

This study presented the following relevant clinical cardiovascular information for treating patients with tricyclic antidepressant overdose.

1 Tachycardia and hypotension were very frequently found in patients with tricyclic overdose. Tachycardia was not solely related to reflex mechanisms induced by systemic hypotension but rather to direct chronotropic effect of tricyclic agents. Systemic hypotension was partially related to relative fluid depletion but peripheral vascular mechanisms also played a very important role. Cardiac failure was not documented in any of the hemodynamically instrumented patients.

2 The most prominent electrophysiologic changes observed appeared to be related to disturbance in conduction and repolarization clinically manifested by AV block, intraventricular conduction defects and prolongation of QT interval.

3 No malignant rhythm disturbances were seen and the 13 patients with ventricular ectopic activity were successfully treated with lidocaine, an antiarrhythmic drug which enhances electrical conduction velocity.

Summary

The cardiotoxicity of tricyclic antidepressants (TCA) was studied in 35 patients admitted to Yale New Haven Hospital for an acute overdose. 23 patients had amitriptyline overdose and 12 patients had imipramine overdose. Twenty seven patients were female and eight were male. Their ages ranged from 13 to 73 years. Twenty patients were receiving TCA chronically and none had prior cardiovascular disorders. Amitriptyline blood levels ranged from 180 to 1560 ng/ml and imipramine blood levels ranged from 150 to 1732 ng/ml.

Tachycardia occurred in 71% and systemic hypotension occurred in 51% of patients. The observed tachycardias were not corrected upon

normalization of fluid and blood pressure derangements. Systemic hypotension was related to relative intravascular fluid depletion and peripheral vascular dilatation. Myocardial failure was not seen clinically or hemodynamically in studied patients.

Electrophysiologic manifestations were those of conduction and repolarization abnormalities: prolonged PR interval in 11%, prolonged QRS complex in 29% and prolonged QT interval in 86% of the patients. No malignant ventricular arrhythmias were documented and only 13 patients had ventricular premature beats which were successfully suppressed with lidocaine infusions.

All cardiovascular manifestations of TCA overdose disappeared when blood levels of TCA reached therapeutic range. Only supportive therapy was utilized in these 35 patients and all patients recovered without complications.

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eter so that it could be placed as near to the ostium of the coronary sinus as possible. Coronary sinus blood flow (CSBF) was measured with a continuous dye injection technique using the following formula

$$\text{CSBF (ml/min)} = \frac{C_i - C_p}{C_p} \times f,$$

where C_i represents the dye concentration (mg/L) of the injectate, C_p is the dye concentration of the plateau (mg/L) in the coronary sinus, and f is the rate of injection (ml/min). The reproducibility of this method had been confirmed by duplicated measurements ($r = 0.988$, $p < 0.001$, $n = 18$) and in addition this procedure might make it more practicable to draw a blood specimen from the coronary sinus when compared with the thermister method.⁹ To confirm whether the blood drawn through the catheter was not contaminated with blood from the right atrium, dye was injected into the femoral vein while recording the dye dilution curve from the coronary sinus. When any contamination was evidenced by an early appearance of dye, the tip of the catheter was further advanced where no reflux appeared from the right atrium. The catheter tip and the contamination test were repeatedly checked before and after every stage of the flow measurement and blood sampling. The stroke work index (SWI) was calculated from stroke index (SI) and left ventricular pressure using the following formula

$$\begin{aligned} \text{SWI (g m/M}^2\text{)} &= \text{SI} \times \\ &(\text{LVSP} - \text{LVEDP}) \times \frac{1.36}{100} \end{aligned}$$

where LVSP = left ventricular systolic pressure and LVEDP = left ventricular end diastolic pressure

The basal hemodynamics were determined at 30 minutes after completing right and left heart catheterizations and 10 ml of blood specimen were withdrawn simultaneously from the coronary sinus and from the aorta for plasma catecholamine assay. Then subjects were asked to perform the isometric handgrip exercise (IHG) at 30% of their maximum voluntary contraction for 3 minutes. Hemodynamic measurements and blood samplings were repeated during the last minutes of the exercise for each subject.

Immediately after the blood specimen was obtained it was transferred into an ice chilled polyethylene tube and plasma was separated by

centrifugation at 3,000 rpm for 15 minutes at 4°C. Each plasma specimen was preserved with one tenth volume of 10% sodium metabisulfite at -20°C until the assay. Plasma catecholamine assay was carried out by our modified procedure of Renzini's original¹⁰⁻¹¹ within a fortnight after blood sampling. This method using an excellent fluorescence spectrophotometer (Hitachi Model MPF 4) installed with a high sensitivity cell assembly (No. 018 0050) permitted accurate measurement of levels as low as 20 to 50 pg/ml of plasma.

All statistical analyses were performed by the Student's paired and unpaired t test. Mean values are expressed in terms of the mean \pm the standard error of the mean.

Results

The hemodynamic determinants before and during IHG are shown in Table II. Of various hemodynamic parameters in the resting condition, cardiac indices lower than 3.00 L/min/m² and LVEDP higher than 13 mm Hg were found in eight and 16 patients, respectively. IHG induced significant increase in heart rate, mean aortic pressure, cardiac output, LVEDP, SWI, and CSBF.

Plasma catecholamine concentrations in individual subjects are tabulated in Table III. There was a close correlation between the values of norepinephrine in the coronary sinus (NE_{CS}) and those in the artery (NE_{A}) (Fig. 1, left panel). The mean value of NE_{CS} in all of the subjects was not significantly different from that of NE_{A} . A significant difference was observed in the levels of both NE_{CS} and NE_{A} among the types of heart diseases. However, when subjects were divided into two groups according to whether they had higher LVEDP than 13 mm Hg or not, NE_{CS} was significantly greater than NE_{A} in subjects with normal LVEDP (331 ± 46 and 241 ± 30 pg/ml, $p < 0.01$) whereas NE_{CS} did not differ from NE_{A} in subjects with elevated LVEDP (243 ± 20 and 267 ± 33 pg/ml). The NE_{CS} were also greater than those of NE_{A} in subjects with normal cardiac output more than 3.00 L/min/m² (280 ± 33 and 232 ± 22 pg/ml, $p < 0.05$) while no significant difference was found in other subjects (295 ± 38 and 318 ± 54 pg/ml).

IHG increased both NE_{CS} and NE_{A} from 285 ± 28 to 465 ± 40 pg/ml and from 241 ± 30 to 416 ± 38 pg/ml, respectively ($p < 0.001$). (F

Norepinephrine levels in the coronary sinus in patients with cardiovascular diseases at rest and during isometric handgrip exercise

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An impaired activity of the cardiac sympathetic nerve may closely participate in the pathophysiological sequence of left ventricular function although its causative or consequential significance remains inconclusive.¹ Among a variety of approaches to evaluate sympathetic nerve activity the biochemical evaluations of plasma catecholamines and serum β hydroxylase activity have been proposed as useful means for clinical purposes.² Currently attention has been directed to measurements of norepinephrine (NE) concentrations in coronary sinus blood as a marker of sympathetic nerve transmitters released from the cardiac tissue.³

The present paper aims to communicate the simultaneous determinations of plasma catecholamine levels in the coronary sinus and in the aorta in subjects with various cardiovascular

disorders and relate them to the functional states of the heart.

Methods

Twenty four patients with various cardiovascular diseases and six with functional murmur were involved in this study. They consisted of 21 males and nine females ranging in age from 13 to 63 years (mean 35 years). Their clinical descriptions are summarized in Table I. None of them had been treated with any sympathomimetic or sympatholytic medication. Informed consent was obtained from each subject after the nature and the purpose of the protocol had been explained.

Diagnostic cardiac catheterization was performed in these patients without any premedication. Left ventricular and aortic pressures were measured through a No. 8F Cordis pigtail catheter connected with a Statham P23Db pressure transducer. Cardiac output was determined by the indicator dilution method using indocyanine green dye. A No. 9F Gensini catheter was introduced from the right femoral vein into the coronary sinus for blood sampling and flow measurement. The tip of the catheter was confirmed by the injection of contrast media through the cath-

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Table 1 Clinical description of all subjects

| Case no | Diagnosis | Age (yrs) | Sex | Class (NYHA) | CTR (%) |
|---------|-----------|-----------|-----|--------------|---------|
| 1 | FM | 17 | F | 1 | 3 |
| 2 | FM | 21 | F | 1 | 47 |
| 3 | FM | 16 | M | 1 | 45 |
| 4 | FM | 16 | M | 1 | 50 |
| 5 | FM | 13 | F | 1 | 39 |
| 6 | FM | 16 | M | 1 | 40 |
| 7 | EH | 38 | F | 2 | 44 |
| 8 | EH | 62 | M | 2 | 52 |
| 9 | EH | 60 | M | 2 | 45 |
| 10 | EH | 63 | M | 2 | 52 |
| 11 | MR | 26 | M | 1 | 50 |
| 12 | MR | 50 | M | 2 | 46 |
| 13 | MS | 39 | F | 3 | 55 |
| 14 | MS | 25 | M | 2 | 49 |
| 15 | AR | 20 | M | 2 | 55 |
| 16 | AR | 58 | M | 2 | 70 |
| 17 | AS | 24 | F | 2 | 54 |
| 18 | AS | 23 | M | 2 | 45 |
| 19 | HCM | 34 | M | 2 | 48 |
| 20 | HCM | 39 | M | 2 | 47 |
| 21 | HCM | 42 | M | 2 | 54 |
| 22 | HCM | 16 | F | 2 | 50 |
| 23 | HCM | 28 | F | 2 | 50 |
| 24 | CCM | 49 | M | 3 | 60 |
| 25 | CCM | 44 | F | 3 | 63 |
| 26 | CCM | 20 | M | 2 | 64 |
| 27 | CCM | 49 | M | 2 | 67 |
| 28 | CCM | 46 | M | 2 | 53 |
| 29 | CCM | 60 | M | 2 | 63 |
| 30 | CCM | 38 | M | 2 | 65 |

Abbreviations: CTR = cardiothoracic ratio; FM = functional mitral regurgitation; EH = essential hypertension; MR = mitral regurgitation; MS = mitral stenosis; AR = aortic regurgitation; AS = aortic stenosis; HCM = hypertrophic cardiomyopathy; CCM = congestive cardiomyopathy.

parallel rises in NE_{cs} .¹⁷ An increased cardiac sympathetic nerve activity induced by exercise has been shown to be associated with an increase in NE_{cs} .¹⁷ Thus NE_{cs} is expected to reflect directly the sympathetic nerve tone of the left ventricle since the coronary sinus blood is mostly derived from that area. However, a significant correlation between the values of NE_{cs} and NE_a was observed in the present study as in our previous observation and those made by others.^{12,17} This may suggest that these values are controlled by the same factors which determine general sympathetic nerve activity. It is also possible that NE_{cs} originates not only from cardiac tissue but from other tissue as well. In this study the mean individual net uptake of E was about 40% both at rest and during IHG and the

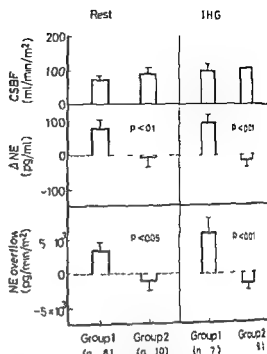


Fig 3 A comparison of coronary sinus blood flow (CSBF), the difference between NE_{cs} and NE_a (ΔNE), and the net NE overflow into the coronary sinus between Group 1 with steep ventricular function curve and Group 2 with a shallower curve. These values are expressed as the mean \pm the standard error of the mean. The mean values of ΔNE during IHG and NE overflow before and during IHG were significantly less in Group 2 than in Group 1.

remaining amounts of E appeared to pass through the coronary circulation. If we assume that a similar percentage of NE escapes from either tissue uptake or metabolic degradation throughout the coronary circulation, NE_a levels may be influenced to a considerable degree by levels of NE_{cs} .

In the present study both NE_{cs} and NE_a did not differ with regard to the types of heart diseases whereas the resting values of NE_{cs} were significantly greater than those of NE_a in patients with normal LVEDP and/or with normal cardiac output. Similar results have been presented in patients undergoing cardiac catheterization,^{12,17} although total catecholamine (NE plus E) levels were lower in the coronary sinus than in the artery.^{12,17} But it seems not worthy that this difference could not be observed in patients with elevated LVEDP and/or low cardiac output. To further clarify the relationship between NE_{cs} and NE_a in various functional states of the heart, we investigated the effect of IHG on both NE_{cs} and NE_a concentrations and

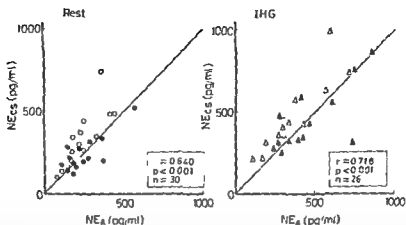


Fig 1 The relationship between NE_{cs} and NE_a at rest and during isometric handgrip exercise (IHG). NE_{cs} significantly correlated with NE_a in both states. The open circles indicate subjects with normal left ventricular end-diastolic pressure (LVEDP) and the closed circles indicate subjects with elevated LVEDP more than 13 mm Hg. The open triangles show subjects with slopes of ventricular function curve of 1.0 or more (Group 1) and the closed triangles show subjects with slopes of less than 1.0 (Group 2).

2) A significant correlation was also observed between the values of NE_{cs} and NE_a during IHG (Fig 1 right panel). When the left ventricular function curve was figured from changes in SWI and LVEDP followed by IHG slopes ($\Delta SWI / \Delta LVEDP$) of 1.0 or greater were found in 13 subjects including six cases of functional murmur (Group 1) while the remaining 13 subjects (Group 2) showed slopes of smaller than 1.0. NE_a in Group 1 was significantly greater than NE_a (458 ± 61 and 363 ± 49 pg/ml, $p < 0.01$) but these respective values did not differ in Group 2 (454 ± 53 and 469 ± 56 pg/ml).

Plasma epinephrine concentrations in the coronary sinus (E_{cs}) were constantly lower than those in the artery (E_a) both before and during IHG ($p < 0.001$). The mean net uptake of E—the arteriovenous difference as a percentage of arterial concentration—was 37.7 ± 2.7 and $39.2 \pm 3.4\%$ before and during IHG respectively. Both values of E_{cs} and E_a significantly increased during IHG (101 ± 11 to 198 ± 26 pg/ml, $p < 0.001$ and 163 ± 18 to 336 ± 38 pg/ml, $p < 0.001$ respectively).

The rate of NE overflow into the coronary sinus was calculated as follows:
NE overflow =

$$CSBF \times (1 - \text{hematocrit}/100) \times \Delta NE$$

where ΔNE represents the difference between NE_{cs} and NE_a . As shown in Fig 3 the mean resting value of NE overflow rate was significantly greater in Group 1 than in Group 2 (3.53 ± 1.31

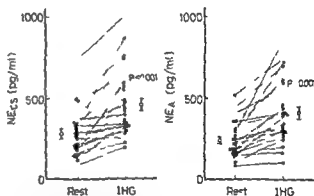


Fig 2 Changes in NE_{cs} and NE_a induced by IHG. IHG significantly increased both values.

and -1.11 ± 1.39 ng/min/M², $p < 0.05$ respectively). The values of CSBF and ΔNE were not significantly different between both groups (70.4 ± 10.4 and 92.2 ± 16.1 ml/min/M² and 82 ± 25 and -8 ± 32 pg/ml respectively). During IHG, ΔNE and NE overflow values were greater in the former group than those in the latter (9.9 ± 25 and -17 ± 15 pg/ml, $p < 0.01$ and 5.99 ± 2.24 and -1.62 ± 0.82 ng/min/M², $p < 0.01$ respectively). CSBF did not differ between both groups (99.4 ± 20.9 and 108.2 ± 18.4 ml/min/M²) during IHG.

Discussion

When cardiac sympathetic nerve fibers were electrically stimulated in the dog experiments the hemodynamic responses were associated with

Table III Plasma catecholamine levels at rest and during isometric handgrip exercise

| Case no | NE _{CS} (pg/ml) | | NE _A (pg/ml) | | E _{CS} (pg/ml) | | E (pg/ml) | |
|---------|--------------------------|------|-------------------------|-----|-------------------------|-----|-----------|-----|
| | R | IHG | R | IHG | R | IHG | R | IHG |
| 1 | 494 | 640 | 420 | 568 | 132 | 240 | 164 | 380 |
| 2 | 88 | 209 | 82 | 110 | 102 | 213 | 206 | 191 |
| 3 | 269 | 404 | 231 | 300 | 169 | 191 | 218 | 349 |
| 4 | 288 | 433 | 221 | 438 | 71 | 114 | 114 | 306 |
| 5 | 158 | 218 | 149 | 167 | 83 | 100 | 179 | 259 |
| 6 | 438 | 475 | 249 | 317 | 109 | 222 | 160 | 376 |
| 7 | 198 | 319 | 177 | 201 | 33 | 50 | 60 | 81 |
| 8 | 494 | 742 | 443 | 712 | 89 | 124 | 155 | 250 |
| 9 | 343 | 449 | 184 | 336 | 113 | 206 | 150 | 353 |
| 10 | 266 | 483 | 244 | 291 | 87 | 56 | 150 | 140 |
| 11 | 286 | 324 | 152 | 273 | 94 | 124 | 99 | 217 |
| 12 | 260 | 255 | 177 | 299 | 79 | 102 | 100 | 145 |
| 13 | 747 | 1006 | 361 | 602 | 185 | 291 | 250 | 477 |
| 14 | 345 | 580 | 333 | 392 | 135 | 203 | 215 | 350 |
| 15 | 192 | 358 | 180 | 300 | 43 | 107 | 117 | 167 |
| 16 | 218 | 310 | 268 | 732 | 181 | 194 | 227 | 677 |
| 17 | 148 | 336 | 141 | 405 | 104 | 236 | 133 | 323 |
| 18 | 205 | — | 362 | — | 250 | — | 463 | — |
| 19 | 142 | 285 | 106 | 248 | 41 | 74 | 48 | 170 |
| 20 | 177 | — | 110 | — | 51 | — | 104 | — |
| 21 | 126 | 351 | 180 | 278 | 39 | 84 | 100 | 160 |
| 22 | 316 | 869 | 292 | 862 | 67 | 713 | 138 | 822 |
| 23 | 204 | 433 | 169 | 463 | 80 | 219 | 114 | 453 |
| 24 | 280 | 333 | 217 | 343 | 274 | 355 | 508 | 570 |
| 25 | 344 | 349 | 355 | 417 | 87 | 140 | 143 | 229 |
| 26 | 164 | 596 | 189 | 406 | 74 | 113 | 147 | 319 |
| 27 | 303 | 756 | 524 | 750 | 120 | 460 | 234 | 818 |
| 28 | 527 | — | 568 | — | 155 | — | 291 | — |
| 29 | 197 | 567 | 309 | 610 | 47 | 166 | 114 | 569 |
| 30 | 200 | — | 250 | — | 60 | — | 9 | — |
| Mean | 284 | 465 | 255 | 416 | 105 | 193 | 173 | 336 |
| SEM | 26 | 40 | 22 | 38 | 11 | 28 | 19 | 38 |
| n | 30 | 26 | 30 | 26 | 30 | 26 | 30 | 26 |
| P | < 0.001 | | < 0.001 | | < 0.001 | | < 0.001 | |

Abbreviations: NE_{CS} = plasma norepinephrine concentration in the coronary sinus; NE_A = plasma norepinephrine concentration in the artery; E_{CS} = plasma epinephrine concentration in the coronary sinus; E_A = plasma epinephrine concentration in the artery; R = rest; IHG = isometric handgrip exercise; SEM = standard error of the mean; — = II vs IHG analyzed by paired t test.

removal rate during the coronary circulation might be reduced in the failing heart. It seems thus that small or negative Δ NE in Group 2 is not due to increased NE_A removal (R). It is also unlikely that the levels of NE_A make the difference in Δ NE between both groups, since NE_A did not significantly differ between Group 1 and Group 2 during IHG. A diminished cardiac NE release from the heart therefore could be the most plausible factor responsible for the small or negative Δ NE. Since coronary sinus blood flow rate might have an influence on the concentration of NE in the coronary sinus, an amount of

NE overflow into the coronary sinus was calculated according to the method of Levy and Blumberg.¹ The rates of NE overflow before and during IHG were also significantly lower in Group 2 than in Group 1.

All of these findings may be compatible with the previous reports that revealed a decreased NE content associated with a reduced catecholamine biosynthesis in the failing heart.¹⁻³ The reduced NE stores may bring about the diminution of its release per nerve impulse and thereby may attenuate the sympathetic nervous support of the failing myocardium.² In this study,

Table II Hemodynamic parameters at rest and during isometric handgrip exercise

| Case no | HR (beats/min) | | Aop (mm Hg) | | CI (L/min/M ²) | | LVDP (mm Hg) | | SWI (g/min/M) | | CSBF (ml/min/M) | |
|---------|----------------|-----|-------------|-----|----------------------------|------|--------------|-----|---------------|-------|-----------------|-------|
| | R | IHG | R | IHG | R | IHG | R | IHG | R | IHG | R | IHG |
| 1 | 66 | 84 | 100 | 125 | 4.01 | 5.54 | 13 | 26 | 81.0 | 111.3 | — | — |
| 2 | 85 | 102 | 100 | 120 | 3.79 | 4.38 | 13 | 15 | 70.0 | 86.8 | — | — |
| 3 | 102 | 120 | 95 | 120 | 6.37 | 8.58 | 5 | 10 | 91.5 | 134.3 | 28.8 | 38.1 |
| 4 | 78 | 108 | 95 | 125 | 5.18 | 6.29 | 10 | 17 | 94.0 | 150.2 | 68.9 | 100.1 |
| 5 | 84 | 96 | 100 | 120 | 4.14 | 4.61 | 11 | 12 | 6.4 | 96.1 | 39.6 | 42.3 |
| 6 | 84 | 96 | 85 | 110 | 6.06 | 5.53 | 11 | 19 | 101.0 | 108.1 | 97.1 | 178.2 |
| 7 | 96 | 114 | 120 | 150 | 3.89 | 5.21 | 9 | 16 | 83.2 | 108.1 | — | — |
| 8 | 66 | 78 | 115 | 130 | 5.29 | 6.21 | 9 | 20 | 197.4 | 218.7 | — | — |
| 9 | 72 | 118 | 100 | 130 | 3.90 | 5.09 | 13 | 16 | 89.9 | 145.6 | 71.3 | 75.6 |
| 10 | 84 | 90 | 110 | 120 | 2.22 | 2.31 | 13 | 15 | 52.5 | 54.2 | — | — |
| 11 | 84 | 102 | 100 | 125 | 4.25 | 5.17 | 20 | 30 | 75.7 | 72.4 | 49.8 | 64.4 |
| 12 | 82 | 138 | 103 | 118 | 1.46 | 1.47 | 4 | 9 | 34.8 | 29.8 | 89.6 | 129.4 |
| 13 | 90 | 120 | 100 | 125 | 3.41 | 3.43 | 10 | 11 | 59.1 | 59.9 | — | — |
| 14 | 96 | 120 | 95 | 125 | 3.55 | 4.64 | 5 | 6 | 57.9 | 82.1 | 86.8 | 100.0 |
| 15 | 84 | 96 | 87 | 105 | 4.33 | 4.59 | 15 | 22 | 84.0 | 96.2 | 113.6 | 163.9 |
| 16 | 68 | 72 | 95 | 120 | 2.87 | 2.90 | 18 | 26 | 103.0 | 107.4 | 211.9 | — |
| 17 | 90 | — | 60 | — | 3.34 | — | 22 | — | 115.0 | — | — | — |
| 18 | 84 | 114 | 92 | 122 | 3.06 | 2.96 | 10 | 15 | 75.1 | 67.2 | 46.9 | 50.4 |
| 19 | 96 | 126 | 85 | 108 | 3.28 | 3.61 | 14 | 17 | 34.2 | 28.7 | 47.0 | 54.9 |
| 20 | 78 | — | 100 | — | 3.61 | — | 29 | — | 80.4 | — | 96.9 | — |
| 21 | 102 | 114 | 125 | 150 | 4.60 | 5.05 | 19 | 17 | 104.3 | 129.1 | — | — |
| 22 | 84 | 126 | 80 | 103 | 3.89 | 3.95 | 26 | 59 | 49.7 | 31.1 | 112.0 | 154.1 |
| 23 | 78 | 114 | 75 | 100 | 4.00 | 4.52 | 27 | 49 | 52.9 | 60.2 | 115.3 | 175.0 |
| 24 | 57 | 66 | 73 | 78 | 1.97 | 1.82 | 23 | 25 | 3.6 | 30.0 | — | — |
| 25 | 66 | 78 | 110 | 140 | 2.55 | 1.77 | 29 | 40 | 25.7 | 21.1 | 91.5 | 97.9 |
| 26 | 96 | 132 | 67 | 85 | 0.83 | 3.15 | 18 | 30 | 27.6 | 30.0 | — | — |
| 27 | 49 | 60 | 70 | 110 | 2.04 | 2.39 | 21 | 32 | 48.0 | 46.3 | 57.4 | 61.5 |
| 28 | 72 | — | 118 | — | 0.75 | — | 30 | — | 45.7 | — | — | — |
| 29 | 80 | 120 | 100 | 135 | 3.18 | 3.72 | 24 | 36 | 48.1 | 49.3 | 107.6 | 191.2 |
| 30 | 66 | — | 83 | — | 3.68 | — | 20 | — | 81.8 | — | — | — |
| Mean | 80 | 103 | 95 | 119 | 3.65 | 4.19 | 16 | 22 | 72.6 | 87.7 | 84.7 | 104.3 |
| SEM | 3 | 4 | 3 | 3 | 0.21 | 0.32 | 1 | 2 | 6.2 | 9.0 | 10.0 | 13.4 |
| n | 30 | 26 | 30 | 26 | 30 | 26 | 30 | 26 | 30 | 26 | 18 | 16 |
| p | < 0.001 | | < 0.001 | | < 0.001 | | < 0.001 | | < 0.01 | | < 0.01 | |

Abbreviations: HR = heart rate; Aop = mean aortic pressure; CI = cardiac index; LVDP = left ventricular end-diastolic pressure; SWI = stroke work index; CSBF = coronary sinus blood flow; R = rest; IHG = isometric handgrip exercise; SEM = standard error of the mean; n = number of cases analyzed by paired t test.

on hemodynamic parameters in this study. It has been well established that the slope of the ventricular function curve induced by IHG flattens with the worsening of cardiac dysfunction.¹¹ When subjects were divided by the slope of the curve (Group 1 and Group 2), NE_{CS} was greater than NE_A in Group 1, but no significant difference was found in Group 2 with the shallow slope of the function curve. The difference between NE_A and NE_{CS} (ΔNE) could be expressed in the following equation: ΔNE (pg/ml) = cardiac NE release into the coronary sinus - $NE_A \times R/100$, where R is the removal ratio (%) of NE during

the coronary circulation. According to this equation, when ΔNE is small or negative, three possibilities might occur: increase in NE_A , increase in R , and decrease in cardiac NE release. If ΔNE is large, the increases and decreases are reversed. To compare the R in the failing heart with a normal heart, Spann and colleagues¹ measured ventricular NE concentration in experimental heart failure produced by aortic constriction in the guinea pig and found that an increment of ventricular NE concentration induced by NE infusion was apparently smaller in the failing heart than in the control heart. This finding suggests that NE

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relatively wide ranging distribution of NE and NE overflow rates was observed in the group of depressed cardiac function. This may be attributable to a variety of patients' conditions studied herein since the physiological and biochemical sequence of cardiac sympathetic nerve function might be under the influence of various factors including severity or duration of cardiac dysfunction, histological changes in the cardiac tissue, coexistent complications, and the past history of the treatment, etc.^{1,22}

In conclusion, the direct measurement of plasma NE level in the coronary sinus and the aorta could be a promising procedure to provide a precise insight into cardiac sympathetic activity in various heart diseases.

Summary

In order to evaluate cardiac sympathetic nerve activity, plasma norepinephrine levels in the coronary sinus (NE_{cs}) and in the artery (NE_a) were determined in 24 subjects with cardiovascular diseases and in six with functional murmur. The resting NE_{cs} was greater than NE_a in 14 subjects with normal left ventricular end diastolic pressure (LVEDP) ($p < 0.01$) and/or in 22 with normal cardiac index ($p < 0.05$), whereas NE_{cs} was not significantly different from NE_a in the remaining patients with elevated LVEDP and/or with reduced cardiac index. Isometric handgrip exercise increased both NE_{cs} and NE_a ($p < 0.001$). When subjects were divided into two groups according to the slope of the ventricular function curve (Δ stroke work index/ Δ LVEDP), NE_a during exercise was greater than NE_a in the group having slopes of 1.0 or more ($p < 0.01$) but neither values significantly differed in the group with slopes of less than 1.0. In the latter group, cardiac NE overflow rate calculated from the difference between NE_{cs} and NE_a multiplied by coronary sinus plasma flow was significantly less than that of the former group before and during handgrip ($p < 0.05$ and $p < 0.01$ respectively). These results suggest that cardiac norepinephrine release into the coronary sinus is reduced in patients with impaired cardiac function.

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Table 1 Energy and current used in relation to the stored energy

| Total stored | Total delivered | Energy (J) | | | Current (amp) | | | |
|--------------|-----------------|--------------------------------|--------|------------------|-----------------|----------------------------------|--------|------------------|
| | | Densities (J/cm ²) | | | Total delivered | Densities (amp/cm ²) | | |
| | | Bastard | Strain | Small Electrodes | | Bastard | Strain | Small electrodes |
| 15 | 9 | 0.8 | 1.6 | 2.9 | 6.2 ± 0.2 | 0.5 | 1.1 | 2.9 |
| 20 | 12 | 1.0 | 2.1 | 3.9 | 10.4 ± 0.4 | — | 1.8 | — |
| 30 | 17 | 1.5 | 3.0 | 5.5 | 13.5 ± 0.4 | 1.2 | 2.4 | 4.3 |
| 45 | 26 | 2.2 | 4.6 | 8.4 | 20.8 ± 0.4 | 1.8 | 3.1 | 8.1 |
| 70 | 40 | 3.4 | 7.0 | 12.9 | 26.6 ± 0.9 | 2.3 | 4.7 | 8.3 |

The effective contact area of the standard electrodes with the hearts of the bastard rabbits was 11.7 cm² for the strain rabbits this area was 17 cm². The small electrodes covered an area of 3.1 cm². These values lead to the presented mean energy and current densities.

Perfusion techniques After anesthetization of the rabbit with sodium pentobarbital (30 mg/kg body weight) and administration of heparin (2500 IU) the heart was excised and subjected to perfusion according to the Langendorff method.¹⁷ Perfusion pressure was held constant at 80 mm Hg and temperature at 36 ± 1° C. The perfusion fluid was prepared according to Meyler¹⁸ with 11 mmol/L glucose as substrate and an ionic composition of (mmol/L): Na 149, K 4.7, Ca²⁺ 1.4, Mg 1.0, Cl 138, HCO₃⁻ 20 and H₂PO₄⁻ 0.4. This medium was equilibrated with a gas mixture of O₂ and CO (95:5) at 37° C and the pH was 7.32 ± 0.05.

Countershock After a 40 minute stabilization period synchronized shocks were given to the beating heart by a Lown type defibrillator (Electrodyne ELD 2). The circular electrodes were placed in transverse direction over both ventricles.

The standard electrodes had a surface area of 110 cm². To test the influence of electrode size (thus density of applied current and energy) on cardiac damage small electrodes were also used (3.1 cm²).

The electrograms necessary for synchronization on the R wave were obtained by two small electrodes (dia 2 mm) stitched onto the epicardium outside the main field of defibrillatory current flow. The shock energy (stored energy) was set by using the panel energy meter of the defibrillator.

The delivered energy was determined by the values of the internal and load resistance. The internal resistance of the defibrillator used was 25 ohms. The resistance of the heart was 33 ± 5 ohms as calculated by peak voltage divided by

peak current. The actual mean delivered energy was 57% of the stored energy (Table I).

The density of the current and energy delivered to the heart depends upon the effective contact area between electrode and heart. Our smaller electrodes were smaller than the smallest hearts used and the effective contact area was equal to the electrode area. This results in the current and energy densities for the small electrodes (Table I). However our standard electrodes were larger than the largest hearts and then the contact area is determined by the heart.

To normalize the contact surface area of the standard electrodes and different hearts we assumed the heart to be an ellipsoid as shown in Fig. 1.

The dimensions were determined on the basis of the heart weight. The real weight (W) at the moment of defibrillation was measured to be 250% of the wet weight. Assuming a specific heart mass of one the volume of the ellipsoid (V) equals W and the axes (a and b) can be calculated if their ratio is supposed to be a/b = 3.2.

$$\text{From } V = (4/3)\pi ab = W \text{ substitution of } b = (2/3)a$$

$$\text{Results in } V = 16/27 \pi a^3 = W \text{ which means}$$

$$a = W \{ (16/27 \pi) \}^{1/3}$$

For hearts with 14.8 gram wet weight the values become W = 37 gram and a = 2.7 cm, and for hearts with 6.3 gram wet weight W = 16.5 gram and a = 1.9 cm.

From these dimensions of the ellipsoid an effective electrode contact area can be calculated. If the electrode is pressed against the heart in such a way that it is positioned at half of the short axis of the ellipsoid (Fig. 1) an elliptic contact area is

Cardiac damage caused by direct application of defibrillator shocks to isolated Langendorff-perfused rabbit heart

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Clinical experience with electrical defibrillation has disclosed that the energy required for successful defibrillation increases with increasing body weight.¹ On the other hand it is known that the occurrence of complications following elective cardioversion is related to the energy content of the pulse.² These findings emphasize the need to gain insight into the critical dose (joules per kg body weight) in pediatric cardiology, as well as in adult cardiology to prevent damage by either too high energy shock or the necessity for repeated shocks in the case of too low an energy level. Thus the need for more effective electrical defibrillation and evaluation of the most ideal wave shape^{3,4} is related to the pulse characteristics and the myocardial damage caused by the electric shock.

Myocardial damage resulting from transthoracic defibrillation shocks has been characterized functionally,^{5,6} morphologically⁷ and biochemically.⁸ Each of these three methods of characterization has its own limitation. Functional changes can be caused by reversible or irreversible cellular changes but damage of individual cells will not always be reflected in decreased cardiac function because the heart may compensate for some dead cells.

Morphological examinations have the disadvantage of defining only visible changes in the area under inspection and may not characterize

functional or physiologic parameters. Release of biochemical substances from cells may indicate reversible as well as irreversible changes although enzyme release appears to indicate cell death.⁹ The present study was undertaken to develop an experimental model to quantify the energy level at which defibrillator pulses damage the heart and to assess parameters potentially related to myocardial injury.

We have chosen to use Lown type counter shocks ranging in stored energy from 15 to 70 joules. The shocks were applied in the synchronized mode thereby avoiding effects of fibrillation on the parameters measured.¹⁰ The electrodes were applied directly to isolated hearts to be certain the current flows through the heart. To avoid deterioration of the heart by lack of coronary circulation the hearts were perfused. Functional, morphological, and biochemical changes were measured in this experimental study in order to combine the advantages of the three methods and to reduce their limitations.

Material and methods

Bastard rabbit hearts with wet weight between 10 and 16 g (average 14 ± 1.6 g) were used. The wet weight was obtained after blotting the heart three times with filter paper. For enzyme release determination the hearts were obtained from Alaska x Wiener F1 rabbits and had a wet weight of 63 ± 0.3 g. The dry weight of these hearts was obtained as $16 \pm 1\%$ of the wet weight from six control comparisons. The total weight of heart and internal perfusion fluid at the moment of the shock was estimated at 25 times wet weight.

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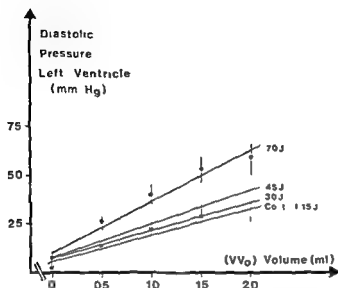


Fig 3 Relationship between left ventricular end diastolic pressure and the filling volume of the heart (V_{Vo}). For the control situation and after 70 J shocks mean and standard error of the mean are presented. The regression lines are shown after shocks with a stored energy of 15 J ($n = 14$, $r = 0.97$), 30 J ($n = 14$, $r = 0.96$), 45 J ($n = 14$, $r = 0.96$) and 70 J ($n = 10$, $r = 0.98$). The number of experiments (n) and the correlation coefficient (r) are within brackets.

cally at 25° C by the method of Rosalki¹⁹ using a kit of Baker Chemicals (Deventer, Holland). To raise the sensitivity in cases of an activity below 12 U/L, the UV CPK reagent of the kit was less diluted so that more effluent could be added to the measuring cuvette with maintenance of the same prescribed end concentrations. A correction was made with the aid of a calibration curve to compensate for low values caused by the introduction of salts from the effluent.²⁰ Potassium determinations were performed with a flame absorption spectrophotometer and the total coronary flow was measured with an electromagnetic flowmeter (Carolina).

Statistical evaluation of data. Regression lines were fitted through the measuring points by the method of least squares and the exactness of the fit was described by the correlation coefficient.

Statistical difference between two groups of measurements was calculated on the basis of the unpaired Student t test. The probability (p) was determined from the Student t value and its corresponding degree of freedom. A p value of 0.05 was regarded as probably significant, while larger values were classified as not significant and lower values were classed as significant.

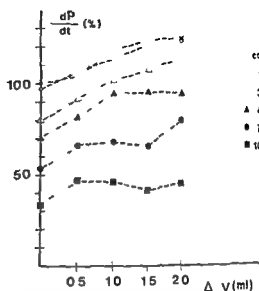


Fig 4 Relationship between time derivative of left ventricular pressure (dP/dt) and the filling volume of the heart (ΔV). The dP/dt is normalized to 100% of its value for the volume prior to shocks. Shocks of 15, 30, 45, and 70 J were given to each heart. The average value for the dP/dt is determined from the individual experiments and is shown in this figure.

Results

Arrhythmias. Many different types of arrhythmias have been seen after defibrillator shocks (Table II). In general, a 15 J shock causes runs of tachycardia and premature beats. Shocks with higher intensity, bradycardia, complete arrest were seen, whereby occurrence and duration of this phenomenon increase with energy. Defibrillator shocks of 70 J often resulted in A-V dissociation, but in other cases the hearts recovered.

A reduction in electrode size resulted in increased current and energy density for the levels of stored energy. In two out of four experiments with these smaller electrodes, observed arrhythmia had a longer duration in comparison with that in the 10 experiments with standard electrodes.

Systolic pressure volume relationship. The systolic pressure volume relationship measured before defibrillator shocks is presented in Figure 5. The curve fits the linear relationship $P_s = 0.5(V_{Vo}) + 65$ (correlation coefficient $r = 0.95$), which P_s indicates the maximum systolic pressure (mm Hg), V the volume of the heart, and V_0 the starting volume. From this it is concluded that the systolic stiffness defi-

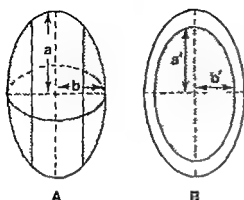


Fig 1 The heart assumed as an ellipsoid in the frontal (A) and lateral view (B). The axes a and b are assumed to have the ratio 3:2. In A the electrodes are applied in parallel perpendicular to the plane of the diagram to make contact halfway b at the borderline of the white and shadowed area. In B the shadowed area represents the contact of the electrode with the heart, which then is an ellipse with axis a' and b' .

results with a and b as the long and short axis of the elliptic area respectively in which $S = \pi a b$. From the ellipsoid volume and the calculated values for a and b it follows that $a = 0.87 a'$ and $b = 0.58 a'$ and so $S = 0.5 \pi a'^2$.

This results in an effective contact surface area of 11.7 cm^2 for the bastard hearts and of 5.7 cm^2 for the hearts of the strain rabbits. Using the total applied energy and current the corresponding densities can be computed. Results are presented in Table I.

Functional studies In order to obtain pressure-volume relationships a balloon free of air connected to a stiff cannula was introduced into the left ventricle via an incision in the left atrium and the mitral valve. One suture was placed just above the mitral ostium to prevent bulging of the balloon out of the left ventricle into the left atrium. The starting volume of the balloon was obtained by opening a three way stopcock connected to the cannula and to the air so that the heart could empty the balloon against atmospheric pressure. The volume of the balloon was increased by injecting an additional 0.5 ml of water via the stopcock until the total added volume was 2 ml. A pressure transducer was connected to the balloon via the stopcock enabling recording and differentiating the left ventricular pressure curve (3 dB 100 Hz). Pressure-volume relationships were determined before and after a defibrillator pulse in steady state which mostly occurred 3 to 5 minutes after the shock.

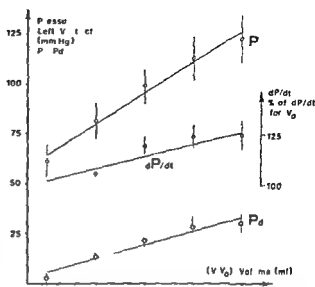


Fig 2 Peak systolic (P_s), end-diastolic (P_d) and time derivative (dP/dt) of left ventricular pressure as a function of filling volume ($V - V_0$) in the control situation. The total volume is V and the starting volume is V_0 . The mean values of the measuring points are indicated and the bars represent the standard error of the mean. The first derivative is expressed as a percentage of that for the starting volume. The regression lines for P ($r = 0.98$), P_d ($r = 0.97$) and dP/dt ($r = 0.9$) are shown.

The shocks were consecutively given to the same heart after completion of the foregoing pressure-volume measurement in the sequence of 15, 30, 45 and 70 J. In some experiments shocks with a similar energy but given in a series were administered to study cumulative effects.

Morphological study For electron microscopic study one synchronized shock (30 or 60 J) was given to each heart and immediately after the shock a fixation solution of glutaraldehyde (1.5%) in 0.09 M phosphate buffer (pH = 7.35) was infused into the coronary system by injecting in the perfusion system just above the aortic cannula. After post fixation in OsO_4 tissue blocks were prepared for electron microscopy. Incisions were made and selected with a light microscope for further examination with a Philips EM301 electron microscope. Gross examination was also carried out in other experiments by cutting open the heart.

Effluent analysis Samples of the effluent perfusate were collected before and at timed intervals after the shock. Dithionitrol was added to the samples (to 10 mmol/L) for protection and the CPK activity was assayed spectrophotometri-

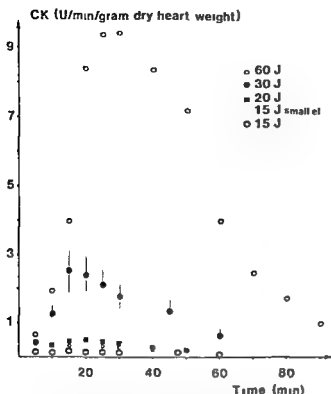


Fig 6 Pattern of CK release after synchronized shocks of 15 ($n = 8$), 20 ($n = 3$), 30 ($n = 11$) and 60 ($n = 1$) joules stored energy. Mean values are indicated and the bars for 30 J shocks indicate the standard error of the mean (omitted for the other shocks because of the small number of measuring points).

following three caused a progressive increase of stiffness up to 17 mm Hg ml^{-1} as the fifth shock had no further influence. One series of 45 J shocks showed a progressive increase of dP/dV with shock number: the first shock raised the stiffness to 17 mm Hg ml^{-1} , the second to 30 and the third to 35 mm Hg ml^{-1} , and the fourth and fifth shock gave no further increase in stiffness.

First derivative of left ventricular pressure. In eight experiments we measured dP/dt as a function of balloon volume (Fig 4). Observation of changes in dP/dt after shocks showed an insignificant decrease in dP/dt for energies of 30 J. A 45 J shock caused a probably significant decrease for all volumes ($p < 0.05$), while 70 J shocks decreased dP/dt to a highly significant degree ($p < 0.005$).

Morphological changes. Gross examination of the ventricles after a 60 J shock revealed a change in tissue near the edge of the electrode which was over the left ventricle. The tissue was pale in comparison to the unaffected muscular tissue. The pale region had a cone shape with the base near the left ventricular electrode and its top

pointing towards the other electrode. The histological microscopic examination of this tissue revealed extensive myofibrillar necrosis. The intercellular spaces were enlarged and contained cellular debris. Electron microscopy showed that myofibrils had an irregular pattern of contraction bands consisting of compressed Z lines which irregularly alternated with overstretched and disrupted sarcomeres. The cell membrane was disrupted over large distances. The mitochondria were swollen and sometimes disrupted while the cristae were broken in most of them (Fig 5).

Electron dense particles, a sign of calcium accumulation, were not seen, not even in the case where we introduced the fixation fluid 15 minutes after the shock instead of immediately allowing time for possible excessive influx of extracellular calcium. Also no lipid droplets were found.

For the lowest energy used (30 J) in these experiments only scattered necrotic cells were found near the electrode, as observed with the light microscope. On an ultrastructural level the cellular alterations are less severe although essentially of the same quality.

Enzyme release. Serial effluent total creatine kinase (CK) activity changes were determined after shocks. In preliminary experiments, determination of lactate dehydrogenase were comparable to CK values, but CK activity showed a more striking increase after shocks due to higher concentration in the myocardium.

Fifteen joule shocks did not elevate CK activity as contrasted with shocks of the same energy but which were applied with smaller electrodes, thus increasing the density of current and energy. The latter caused a moderate although not significant elevation, just like the 20 J shocks indicating a small number of irreversibly damaged cells. The increase in CK activity after a 30 J shock was significant ($p < 0.005$). The summarized results in Fig 6 show a maximum CK activity 15 to 20 minutes after this shock. Higher energy resulted in severe damage underlining a relationship between dose and damage.

The simple contact between defibrillator electrodes and heart without applying a shock gave no increase of CK activity. Elevation of medium temperature to 42 degrees centigrade in steps of $1^\circ \text{C}/10$ minutes and subsequent lowering to normal temperature in one experiment caused significant increase of CK activity but merely a seventh of the value after a 30 J shock.

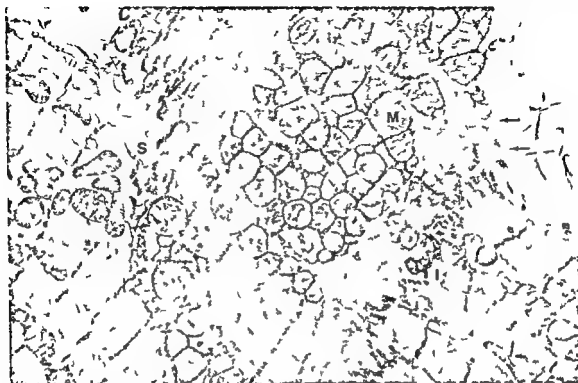


Fig 5 General view of damaged cardiac cell membrane. Z lines have been compressed in contraction bands (arrows) while other sarcomeres have been overstretched and disrupted. I = intercalated disc. S = intercellular space. M = mitochondrion.

dP_s/dV for the used bastard rabbit hearts is 31 mm Hg ml⁻¹. The systolic pressure volume relationship did not change significantly ($p < 0.05$) after shocks with energy from 15 to 70 J.

Diastolic pressure volume relationship. The diastolic pressure (P_d) volume relationship measured before defibrillator shocks is presented in Fig 2. The regression line through the measuring points is $P_d = 14(V/V_0) + 11$ (correlation coefficient $r = 0.97$). From the slope of this line it can be concluded that the diastolic stiffness dP_d/dV is 14 mm Hg ml⁻¹.

Defibrillator shocks of 15 or 30 J stored energy did not influence this stiffness (Fig 3). But after 45 J shocks we found a mean diastolic stiffness of 17 mm Hg ml⁻¹ although the increase was not significant as was seen from the unpaired Student *t* test. After 70 J shocks however a significant ($p < 0.025$) increase of the diastolic stiffness to 26 mm Hg ml⁻¹ was observed. Fig 3 shows the results. It should be emphasized that these results are obtained in identical series for each rabbit: the first shock being 15 J, the second 30 J, the third 45 J, and the fourth 70 J. Thus consecutive shocks with increasing energy were

Table II Disturbance of the heart rhythm after shocks with varying energy

| Energy (J) | Duration of disturbance (sec) | Duration of arrest (sec) | Arrhythmia in number of experiments | | | | |
|------------|-------------------------------|--------------------------|-------------------------------------|---|---|---|---|
| | | | O | P | T | B | A |
| 15 | 15 ± 4 | — | 2 | 7 | 4 | 0 | 0 |
| 30 | 37 ± 13 | 13 ± 4 | 1 | 5 | 1 | 1 | 5 |
| 45 | 72 ± 29 | 39 ± 14 | 0 | 4 | 4 | 3 | 0 |
| 70 | > 300 | 83 ± 19 | 0 | 2 | 2 | 6 | 7 |

The duration of the disturbance was measured as total recovery time to sinus rhythm. The duration of the arrest was measured from the shock to the first ventricular electrical complex. The arrhythmia has been classified (fourth column) as: O = 0 premature beats; P = tachycardia; T = bradycardia; B = and complete ventricular arrest; A. The occurrence of dysrhythmias in combination makes the total term in a row unequal to the total number of 10 observations.

given. To study the influence of consecutive shocks one series consisting of five shocks with the same energy was also given to one heart. One series of 15 J shocks did not alter dP_d/dV significantly. In one series of 30 J shocks the first shock caused no increase of stiffness but the

caused by parasympathetic nerve stimulation^{15, 16} The duration of the arrest induced by excessive nerve stimulation however is constant and no function of shock intensity¹⁵ In addition to enhanced nerve activity, the shock depolarizes the cell directly by massive charge transfer as demonstrated by Jones and colleagues²¹ for cultured heart cells

In concluding we would like to state that arrhythmias observed after a shock are indicators for changes in cellular electrical equilibrium They may be caused indirectly by released nerve transmitters but are more likely caused directly by the shock which may depolarize cardiac cells moderately leading to tachyarrhythmias or severely resulting in bradyarrhythmias or arrest

The first signs of disturbed electrical functioning of the heart were seen after 15 J shocks applying an energy density of 0.8 J/cm² and a current density of 0.5 amp/cm

Not only the electrical but also the mechanical functioning was changed after shocks An increase in diastolic stiffness and a decrease in dP/dt was noticed while the systolic stiffness was unchanged An increase in diastolic stiffness for the same diastolic volume means a higher pressure This higher pressure can only be built up by an increased wall tension This indicates that diastolic relaxation is not complete and that the myofibrils are contracted to a certain degree during diastole This is also shown histologically Our electron microscopic observations showed contracture bands in myofibrils meaning that relaxation is not complete During contraction the myofibrils on the average seem to build up the same tension since the systolic stiffness is not altered by the shock meaning that for a given volume the same pressure is built up That this increase in diastolic pressure means a change in mechanical functioning was further shown by a decrease in the time derivative of left ventricular pressure Since preload was controlled and the hearts were beating isovolumically the contractility seems to be decreased by the shock²² This may be explained by the fact that the myofibrils in the contracture band only take part in contraction for a small portion or not at all Thus fewer myofibrils can be fully activated

A critical remark should be made about our control values for the systolic and diastolic stiffness Our values are approximately a factor 10 higher than those reported for dog hearts²³

This may be explained by the Laplace law which describes the relationship between wall tension and pressure in a hollow organ as a function of geometry and size From this law there follows an inversely proportional relationship between stiffness and volume Since the rabbit hearts we used are considerably smaller than dog hearts it may lead to higher stiffnesses in our case Also we did not find an exponential relationship between volume and pressure as did Glantz and Kerner²⁴ We used only moderate volumes for which the curve is also linear Another factor may be that they used non perfused isolated hearts instead of beating hearts as in this study

Our results indicate a change in mechanical functioning if the energy exceeds 45 joules or a density of 1.5 J/cm² and a current density of 1 amp/cm However this result was obtained in a series of shocks and the 45 joules was preceded by a 15 joule and by a 30 joule shock The study of the influence of consecutive shocks showed in a series of only 45 J shocks a progressing increase in diastolic stiffness with shock number affirming the known correlation between necrosis and repetition of shocks The preceding shocks probably make the heart more susceptible to damage²⁵

Besides electrical and mechanical functioning we also measured some biochemical parameters The coronary flow rate was temporarily increased after 15 and 30 joule shocks Since the coronary flow rate is known as a determinant of oxidative metabolism in isolated perfused hearts this suggests a temporarily increased oxygen demand by the heart Tentatively the vasodilation probably mediated by adenosine from ATP degradation can be explained by a response of the heart to shocks by ATP consuming processes to return to the normal situation comparable to normal physiological response to enhanced exertion Shocks also caused an increased effluent to creatine kinase (CK) activity Enzyme depletion appears to be a biochemical indicator of the extent of myocardial damage The enzyme release increased in value with increasing shock energy indicating a relationship between shock intensity and damage The increased CK level after shocks with the same 15 J stored energy but applied through smaller electrodes shows that higher densities of current and energy are more damaging than total applied current and energy energy and current per gram heart weight

Since energy may damage the heart by heating

Local temperature effects were less plausible because preliminary studies had shown that after 30 J shocks with saline soaked gauze covered electrodes improving the electrode heart contact CK activity was rather higher than lower in comparison with bare electrode shocks

Potassium Potassium depletion could be detected in the initial 40 seconds after both 15 and 30 J shocks by an increase from 4.7 to at most 5.1 mmol/L in 10 second samples ($n = 3$). Then the potassium surplus was washed out by increased flow making the differences with the initial concentration too small for measurement with the technique used

Coronary flow Simple pressing of the electrodes against the heart resulted in a small elevation of coronary flow rate. After shocks flow decreased the first minute. This decrease was larger for a shock induced temporary arrest than for a tachyarrhythmia. The flow rate subsequently rose above the starting value between the second and fourth minute followed by a gradual return to the starting flow (Fig 7). This overshoot was higher for larger shocks.

Discussion

Defibrillation pulses undoubtedly cause alterations in the electrophysiology and mechanical function of the isolated perfused rabbit heart. Since our first goal was to develop an experimental model to study cardiac damage and to assess related parameters we shall first discuss our data relative to that

Many causes may influence a heart in an experimental defibrillation study but by using an excised perfused heart we could control coronary perfusion pressure, PO of the perfusate, temperature, afterload, preload and we could avoid the influence of anesthetic agents and reduce neural influence. By applying synchronized shocks the effects of fibrillation could be avoided. Although this model gives more control it is even further away from the normal physiological situation than an anesthetized animal is. But it is useful to determine damage levels or compare damage caused by different shocks.

The changes in parameters we used to assess damage caused by the shock require the following discussion.

The duration of disturbance of the rhythm increased with shock energy but also the character of the disturbance changed since for moderate

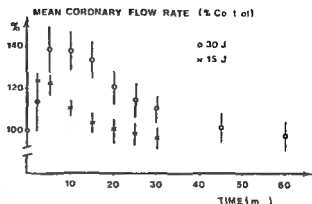


Fig 7 Mean coronary flow rate as a percentage of the control value prior to the shock after 15 ($n = 8$) and 30 ($n = 11$) joule shocks presented as a function of the time elapsed after shocks. Mean values and standard error of the mean are indicated.

shocks only some premature beats and short runs of tachycardia were noticed and for heavy shocks mostly a long duration arrest was seen.

Those arrhythmias may be caused by a direct depolarizing action of the shock¹¹ or by activation of nerve endings which may lead to changes in resting potential.

Temporary changes in resting potential alter the permeability of the membrane to ions or vice versa. The observed increase in extracellular potassium concentration after shocks indicates that the membrane has become more permeable to K ions which supports the idea of a change in membrane potential towards depolarization. A moderate change in resting membrane potential may result in one premature beat if it lasts briefly or a run of tachycardia if the duration of the partial depolarization is longer. No conclusive evidence exists about the cause of this partial depolarization. It may be caused by the shock directly since the current being an ionic current in the heart requires a large amount of moving ions. These transported ions may give rise to imbalances in electrical cell equilibrium resulting in a changed excitability. But stimulation of sympathetic nerve endings may also change the cell's electrical equilibrium by release of transmitter acting on the membrane.

A strong shock gives a long lasting arrest its duration increasing with shock energy. This arrest may be caused by a total and enhanced depolarization after the shock which renders a cell inexcitable for the duration of the depolarization. The enhanced depolarization is partly

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the effect of increased heart temperature on CK activity was also studied. An increase of the perfusate temperature to 42° C caused significant CK activity. To induce this temperature rise by shock energy it would require 158 J (6° C \times 63 g heart) which is a factor 7 higher than the energy caused by the shock. Thus it is not probable that the damage is caused by heating.

The biochemical parameters indicate the first signs of detrimental influence of the shock intensity is a 21 J/cm² density or a current density of 18 amp/cm².

Although we could demonstrate a change in parameters describing electrical or mechanical functioning of the heart and some biochemical parameters the difficulty remains to define damage because there are reversible, irreversible and intermediate phases⁹ and because reduction of tissue function may be caused by total failure and/or partial failure of cells. In addition as a consequence of heterogeneity of the heart muscle destroying of cells of one type can be functionally more effective than death of the same amount of cells from other cardiac types. Nevertheless without being able to describe a sharp borderline between damaged reversibly damaged and undamaged areas for the total heart we can conclude from this study that defibrillator shocks may at least temporarily change cardiac function. The first signs are seen at an energy density level of 0.8 J/cm² and accompanying current density of 0.5 amp/cm. At levels of 21 J/cm² and a current density of 18 amp/cm² cellular damage could be proven as indicated by enzyme release.

Extrapolating experimental results to the clinical environment has to be done very carefully. From this study it would have been omitted if there was not the tendency to raise the defibrillator output for heavy subjects¹⁰ whereas in pediatric cardiology no uniformity in dose concept has been attained.¹¹

On the basis of the above mentioned damaging doses no cardiac damage may be expected for normal internal defibrillation with energy up to 50 J and electrodes of 60 cm² size.

For external defibrillation the applied energy density is unknown. Assuming the current density at the apex electrode (60 cm²) equals that in the part of the heart just below it, normal external adult defibrillation using 400 J as the maximum energy seems to be safe using for instance 1000 J may result in 15 amp/cm² which

in this study induced bradyarrhythmias. In pediatric cardiology even the normal range up to 400 J may result in excessive energy density to the smaller electrodes (e.g. 15 cm²). Estimation in advance of the tolerable energy for each electrode before its application seems to be recommended.

Summary

The purpose of this study was to establish the damaging dose of defibrillator pulses. The damage caused to isolated perfused rabbit hearts by synchronized defibrillator shocks with a stored energy from 15 up to 70 joules is reported. The damage was characterized by the duration and severity of post shock arrhythmias, changes in the elastic properties of the left ventricle, the first derivative of left ventricular pressure, morphological changes of the heart muscle, elevation of creatine kinase, potassium washout and a change in mean coronary flow rate. Varying the electrode area showed that densities of applied current and energy are major factors in damaging the heart.

At current and energy densities of 0.5 amp/cm² and 0.6 J/cm² respectively, potassium washout and mild arrhythmias are seen as is complete arrest of the ventricles at 1.2 amp/cm² and 1.5 J/cm² pulses. After 1.8 amp/cm² irreversible cell damage occurs as demonstrated by CK release and also cardiac function is reduced, measured by increased diastolic stiffness and decreased contractility. Current and energy densities exceeding 2.5 amp/cm² and 4.2 J/cm² respectively cause changes in cardiac function incompatible with life. Accumulation of damage was observed with a series of 1.2 amp/cm² shocks.

We are indebted to H. P. Tromp, M.D. for carrying out preliminary experiments, to F. A. Bekus for technical assistance and to Mrs. A. E. Schwartz for preparing the manuscript. The morphological examinations were done at the Department of Electron Microscopy of the Free University Amsterdam directed by Mrs. E. C. M. Hoefnagel, Ph.D. who also interpreted the microscopic findings. We gratefully thank G. J. Anderson, M.D. Philadelphia for his valuable discussions.

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Table 1 Patient values for baseline VPB frequency and complexity and study VPB frequency complexity, and serum quinidine levels

| Baseline | | | | | Study | | | | | |
|----------|-----------|------------|------------------------|----------------|---------------|-----------------------|-------------------------------|---------------------------------------|----------------------|------------------------|
| Patient | Age (yrs) | Q dose | VPB frequency (bts/hr) | VPB complexity | Response to Q | VPB complexity* | Lowest VPB frequency (bts/hr) | Serum Q range during response (µg/ml) | Peak serum Q (µg/ml) | Trough serum Q (µg/ml) |
| A | 62 | 200 mg q6h | 480-1800 | M/P | N | None | 16-94 | — | 1.95 | 1.55 |
| B | 38 | 200 mg q6h | 720 | P/VT | Y | 4M/1P | 14-11 | 0.88-1.44 | 1.44 | 0.58 |
| C | 67 | 200 mg q6h | 600-2400 | M/P | Y | 2M/1/2P | 52-40 | 0.72-1.28 | 1.65 | 0.65 |
| D | 60 | 200 mg q6h | 45-205 | M/P | Y | 1/2P | 0 | 2.90-4.50 | 4.50 | 2.50 |
| E | 66 | 200 mg q6h | 30-120 | M/VT | Y | None | 0 | 1.50-2.10 | 2.10 | 1.50 |
| F | 65 | 200 mg q6h | 480-600 | None | Y | None | 0 | 3.17-5.07 | 5.07 | 3.17 |
| G | 50 | 200 mg q6h | 180-300 | P | Y | None | 0 | 2.20-3.40 | 3.40 | 2.20 |
| H | 61 | 200 mg q6h | 900 | M/P | N | 5-1/2M/ 1 1/2VT 6P | 184-146 | — | 2.50 | 1.89 |
| | | 300 mg q6h | 900 | M/P | Y | 2 1/2M/ 1 1/2P | 0 | 2.80-4.25 | 4.25 | 2.80 |
| I | 45 | 300 mg q6h | 300-720 | M/P | N | 4M/2 1/2P | 124-58 | — | 2.15 | 1.38 |
| J | 81 | 300 mg q6h | 900† | None† | Y | None | 0 | 3.60-5.45 | 5.45 | 3.60 |
| K | 60 | 300 mg q6h | 720-900 | None | Y | None | 0 | 2.14-4.17 | 4.17 | 2.14 |
| L | 81 | 300 mg q4h | 120-500 | P/VT | Y | 1M/2P | 8-8 | 5.27-5.92 | 6.17 | 5.27 |
| M | 62 | 400 mg q6h | 600‡ | M/P‡ | Y | 5 1/2M/3P 2 1/2VT | 14-14 | 4.15-4.75 | 5.10 | 3.0 |
| N | 46 | 400 mg q6h | 300-600 | None | Y | None | 0 | 2.46-2.82 | 2.82 | 1.60 |

Abbreviations: M = multiform; N = no; P = pairs (two VPBs in succession); Q = quinidine; VPB = ventricular premature beat; VT = three or more VPBs; Y = yes.

† = VPBs absent throughout study

‡ = Baseline observations obtained after discontinuation of quinidine

§ = Baseline observations obtained while patient was receiving quinidine 300 mg every 6 hours

|| = Occurrence of complex form of VPB at any time during baseline observations

¶ = Number of hours during down interval in which a particular complex form of VPB was noted

||| = In patients without complete VPB suppression for at least one half hour interval, the values given are for the two consecutive half hours lowest VPB frequency

miscellaneous forms of heart disease. Four patients were in New York Heart Association Functional Class 3 or 4. Ten patients were being treated with digoxin and one with propranolol.

All patients studied were hospitalized in the Coronary Care Unit of the Baltimore Veterans Administration Medical Center. In 12 of the 14 patients, oral quinidine sulfate was being initiated for the treatment of sustained ventricular arrhythmias. In one patient (Patient J) quinidine was being discontinued because of the apparent cessation of ventricular arrhythmias after a ventricular demand pacemaker had been inserted to treat episodes of marked sinus bradycardia (33/minute) secondary to 2:1 sinoatrial block. In another patient (patient M) with persisting ventricular ectopy at a quinidine dose of 300 mg every 6 hours, the dose had been increased to 400 mg every 6 hours. In all cases the dose of

quinidine was selected by the physicians responsible for the clinical care of the patient. Written informed consent was obtained before the patient was entered into the study.

Serum quinidine concentration was determined immediately before and at 1, 2, 3, 4, 5, and 6 hours after the study dose of quinidine. The quinidine assay employed was a specific immunochemical method recently developed by one of us (WGC).¹⁰

The dose of quinidine was 200, 300, or 400 mg every six hours in 13 patients and 300 mg every four hours in one patient. One patient was at both 200 mg and 300 mg every six hours to insure that a steady state had been attained before patients received quinidine for at least five lives prior to the study. The mean interval between baseline observations and initiation of quinidine therapy was 18 days (range 1

Relation of ventricular premature beat suppression to serum quinidine concentration determined by a new and specific assay

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Ventricular premature beats (VPBs) have been identified as a risk factor for sudden death. Sudden death is most often the result of ventricular fibrillation. Although it has not been established that long term antiarrhythmic therapy can prevent ventricular fibrillation, clinicians frequently employ antiarrhythmic drugs to suppress VPBs in the hope that the risk of sudden ventricular fibrillation will be decreased. Although there is little question that quinidine suppresses VPBs effectively in many patients,^{1,2} it is not clear to what extent determination of the serum quinidine concentration can assist the clinician in planning optimal quinidine therapy.

The present study explores the relationship between serum quinidine concentration and VPB frequency. The quinidine assay employed is a high performance liquid chromatography (HPLC) method recently developed in our laboratory that is specific for quinidine.^{3,4} Earlier quinidine assays lacked specificity and measured in addition to quinidine dihydroquinidine and a multitude of metabolites of unknown activity. For example, the widely used assay of Brodie and Udenfriend^{5,6} which measures total fluorescence

after precipitation of plasma proteins yields quinidine concentrations approximately twice those of the more specific extraction assay methods.^{1,2} Thus it has recently been pointed out that the relationship between serum quinidine concentration and therapeutic effect should be reassessed using more specific quinidine assays.⁷

In a prior study utilizing the new HPLC assay we assessed the pharmacokinetic properties of quinidine in a group of hospitalized patients who were receiving the drug for the suppression of ventricular arrhythmias.⁸ As a part of that study serum quinidine concentrations were determined hourly during a dosage interval at steady state while the cardiac rhythm was documented by continuous Holter monitor tape recording. VPB frequency and complexity prior to the initiation of quinidine therapy had been established by Holter recording or computer assisted oscilloscopic monitoring. We applied the rigorous criteria recently proposed by Winkle⁹ to distinguish a true drug response from spontaneous variation in ventricular ectopy and identified the range of serum quinidine concentrations that were associated with a therapeutic response defined in this manner.

Methods

Fourteen patients (all males) are the subject of the present report (Table I). Their ages ranged from 45 to 81 years with a mean age of 62 years. Eight patients had chronic ischemic heart disease. Two patients had cardiomyopathy and four had

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Results (Table I)

There was a therapeutic response to quinidine in 12 of 14 patients. In four of these 12 patients there was total VPB suppression. The remaining eight responders demonstrated 90% VPB suppression that persisted for at least two consecutive half hour segments during the steady state dosing interval of 4 to 6 hours. Four of these eight patients had no VPB's during at least one half hour segment of the dosing interval.

In the ten patients who did not have total VPB suppression at steady state we looked for a correlation between serum quinidine concentration and VPB frequency. (Since patient H was studied at two dosage levels 11 dosing intervals were analyzed.) Considering the ten patients as a group we could find no correlation between serum quinidine concentration and VPB frequency during the dosing intervals at steady state. The mean serum quinidine concentration at the time of the lowest VPB frequency during the dosing interval ($2.93 \pm 1.48 \mu\text{g/ml}$) did not differ significantly from that at the time of highest VPB frequency ($2.77 \pm 1.56 \mu\text{g/ml}$). However in seven individual dosing intervals there was a tendency for VPB frequency to decrease as the serum quinidine concentration increased.

We compared the seven steady state dosing intervals in which at least one half hour segment was completely free of VPB's with the remaining eight dosing intervals in which there was no half hour that demonstrated complete suppression. Both the mean and peak serum quinidine levels tended to be higher for the dosing intervals with at least one half hour of complete VPB suppression (mean = $3.14 \pm 0.87 \mu\text{g/ml}$, peak = $3.97 \pm 1.13 \mu\text{g/ml}$) than for those with out this finding (mean = $2.55 \pm 1.78 \mu\text{g/ml}$, peak = $3.00 \pm 1.86 \mu\text{g/ml}$). However these differences were not statistically significant.

Multiform VPB's were present in eight responders at baseline but were absent in these patients in 47% of the half hour segments monitored during steady state therapy. Paired VPB's were present in nine responders at baseline but were absent in 68% of the half hour segments at steady state. Salvos of three or more VPB's were present in three responders prior to quinidine therapy but did not occur in any of the half hour segments monitored during therapy in these three patients.

Using the new HPLC quinidine assay the

range of serum quinidine concentrations associated with a therapeutic response at steady state in our patients was 0.72 to $5.92 \mu\text{g/ml}$. Three of the 12 responders demonstrated a response at serum levels of less than $2.0 \mu\text{g/ml}$ and two of the three responded at a level of less than $1.0 \mu\text{g/ml}$. During the three dosing intervals in which definite therapeutic response to quinidine could not be identified the serum quinidine concentrations ranged from 1.38 to $2.50 \mu\text{g/ml}$.

Patient H was studied after the initial 300 mg dose of quinidine and at steady state at doses of 200 and 300 mg every 6 hours. Fig 1 demonstrates the lack of a response after the initial 300 mg dose (mean serum $Q = 0.84 \mu\text{g/ml}$). On a regimen of 200 mg every 6 hours a response could not be documented at steady state (mean serum $Q = 2.09 \mu\text{g/ml}$) however when the dose was increased to 300 mg every 6 hours there was clearly a response at steady state (mean serum $Q = 3.50 \mu\text{g/ml}$).

Discussion

In order to assess the usefulness of serum quinidine concentrations in the management of patients with ventricular arrhythmias the following conditions should be met:

1. The quinidine assay employed should be specific for quinidine and should not include contaminants and metabolites. Unfortunately many earlier studies employed assays that were not specific for quinidine.^{2, 8, 11, 17, 18}

2. There should be a quantitative estimate of the degree of VPB suppression. It is of interest that some of the reported therapeutic ranges for quinidine concentration were determined solely in patients with atrial fibrillation.¹ In those studies which deal with the response of ventricular arrhythmias to quinidine therapy various criteria have been used to determine efficacy. For example Kessler and associates¹¹ considered a

decrease in premature contractions to be evidence of clinical effectiveness but no data are provided concerning VPB frequency either before or during quinidine therapy. Gaughan and colleagues⁸ studied the response to a single 0.6 g dose of quinidine. They defined a positive response as a 50% or greater reduction in VPB and abolition of repetitive beats. However it has recently been pointed out that because of the marked spontaneous variation in the degree of ventricular ectopy,¹ a 90% reduction in VPB

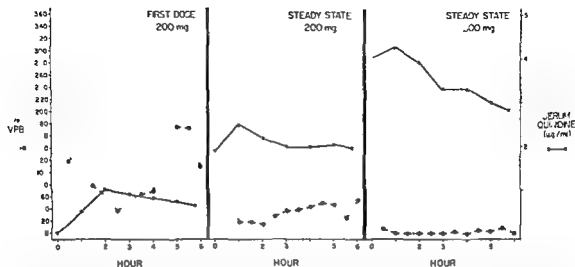


Fig 1 Serum quinidine concentration (solid line) and percent of baseline ventricular premature beat (VPB) frequency (dotted line) in Patient H during a 6-hour dosing interval after the initial 200 mg of quinidine at steady state on a regimen of quinidine 200 mg every 6 hours and at steady state on a regimen of quinidine 300 mg every 6 hours. A therapeutic response to quinidine as defined in this paper = present only at a dose of 300 mg every 6 hours.

days) The mean interval between baseline observations and observations at steady state was 5.8 days (range 2 to 14 days)

Winkle's criteria⁴ were used to determine if a therapeutic response to quinidine was present. During steady state quinidine therapy there had to be complete VPB suppression for a half hour or 90% suppression compared to the baseline frequency that was maintained for at least two consecutive half hour segments of the dosing interval. When the recorded baseline VPB frequency varied the lowest frequency was used in the calculation of percent suppression at steady state. The results were analyzed to determine the range of serum quinidine concentrations that was associated with a definite therapeutic response.

Baseline VPB frequency and complexity were determined by Holter monitoring in three patients and by computer assisted CCU oscillographic monitoring in 11 patients. In all 14 patients cardiac rhythm was recorded on a Holter monitor during the steady state dosing interval selected for study. Sequential 30 minute segments of the recording were analyzed to determine the total number of VPBs in each segment. Each half hour segment was also analyzed for the presence or absence of the following complex forms of VPBs: multiform pairs and salvos of three or more.

In the 12 patients being started on quinidine baseline observations of VPB frequency and com-

plexity were made prior to the start of quinidine therapy. In patient J the baseline was established after the discontinuation of quinidine. In patient M the baseline was established at a dose of 300 mg every 6 hours and the study was carried out at a dose of 400 mg every 6 hours.

In the 14 patients who are the subject of the present report the baseline VPB frequency ranged from 30 to 2400 per hour. In only two of the patients was the lowest recorded baseline VPB frequency less than 60 per hour. In these two patients (Patients D and E) VPB frequency ranged from 45 to 205 per hour and from 30 to 120 per hour respectively. Because the VPB frequency in these patients most often was greater than 60 per hour they are included along with the other 12 patients in the analysis of therapeutic response. Thus an average baseline VPB frequency of at least one per minute was required for inclusion in the study.

The effect of quinidine on complex forms of VPBs⁵ was assessed in the patients who were classified as responders according to Winkle's criteria. For those responders with multiform VPBs, pairs or salvos of three or more VPBs at baseline we determined the percent of half hour segments during the steady state quinidine dosing interval in which each of these complex forms was absent.

Data were analyzed using non paired t tests and linear regression analyses.

be shown for an entire patient group there appears to be a tendency in individual patients for VPB frequency to be lower at higher serum quinidine levels. Therefore if VPBs are not controlled at a serum quinidine level within the therapeutic range the dose may be increased unless there is evidence of quinidine toxicity.

Summary

Fourteen patients who were receiving quinidine in doses of 800 to 1800 mg per day for ventricular arrhythmias underwent Holter monitoring during a steady state dosing interval at a mean of four days after the initiation of quinidine therapy. Serum quinidine concentration determined by a specific high performance liquid chromatography method was measured hourly during the dosing interval. Ventricular premature beat (VPB) frequency during quinidine therapy was compared to the baseline VPB frequency. A reduction in VPB frequency of at least 90% was required to substantiate the presence of a therapeutic response to quinidine.

In 12 of the 14 patients a therapeutic response to quinidine was present at serum levels ranging from 0.72 to 5.92 $\mu\text{g/ml}$. There was no group correlation between serum quinidine concentration and VPB frequency but there was a tendency in individual patients for VPB frequency to decrease as serum quinidine level increased. Quinidine toxicity was not observed in these 14 patients.

Because of the wide variation in response to quinidine a serum quinidine concentration that is within the therapeutic range is not necessarily the optimal serum quinidine concentration for an individual patient. The clinician may therefore consider increasing the dose if there is no evidence of quinidine toxicity and the ventricular rhythm disturbance is not adequately controlled.

We wish to express our appreciation to Ms. Georgette Frank and Mr. Gary Shayne for their expert technical assistance and to Mrs. Helen Spencer and Mrs. Patricia Wemel for typing the manuscript.

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frequency should be required to substantiate the presence of a true drug effect.¹⁴

Quinidine assay The quinidine assay used in this study is a new and specific HPLC method¹⁵ which excludes the known metabolites of quinidine. Although there is evidence that these metabolites may have antiarrhythmic activity in mice and rabbits, activity has not yet been demonstrated in man, and in man the serum concentration of these metabolites is generally below that of quinidine.¹⁶

Analysis of therapeutic response The marked spontaneous variability of ventricular arrhythmias has been emphasized recently by a number of investigators.^{17,18,20} This factor must be taken into account before an observed decrease in ventricular ectopic activity can be accepted as evidence of a drug effect. Winkle¹ has recently proposed rigorous criteria which are applicable in the clinical setting to differentiate a true drug response from spontaneous variation in VPB frequency. These criteria were met in 12 of the 14 patients in the present study. For the patients classified as responders according to Winkle's criteria, complex forms of VPBs (multiform pairs or salvos of three or more) present during baseline observations were absent in from 47% to 100% of the half hour intervals monitored during steady state therapy. As there appears to be even greater spontaneous variability in VPB complexity than in frequency,¹⁸ a decrease in complex forms during quinidine therapy was not considered sufficient in itself to establish the presence of a therapeutic response.

Relationship between serum quinidine level and VPB suppression Because of the marked differences that exist among patients with arrhythmias, our failure to demonstrate a correlation between serum quinidine level and VPB frequency in the entire group of patients is not surprising and is consistent with the experience of other investigators.^{1,6} As each patient was not studied at multiple dosage levels, we cannot comment on whether a dose response relationship would pertain in individual patients. In patient H (Fig 1) such a response was demonstrable. It is of interest that both mean and peak serum quinidine levels tended to be higher during dosing intervals with at least one half hour of complete VPB suppression than in dosing intervals without this finding, and in seven of 11 steady state dosing intervals there was a tendency for VPB

frequency to decrease as serum quinidine level increased.

The range of therapeutic serum quinidine concentrations extended from 0.72 to 5.92 $\mu\text{g/ml}$. No patient in the present study manifested quinidine toxicity, but one patient seen in consultation demonstrated new intraventricular conduction defects at an estimated peak serum quinidine concentration of 6.3 $\mu\text{g/ml}$. Three patients responded at levels of less than 2.0 $\mu\text{g/ml}$, and two of the three responded at a level of less than 1.0 $\mu\text{g/ml}$. Lown's group²¹ has also described patients who show a therapeutic response to quinidine at serum levels of less than 2.0 $\mu\text{g/ml}$.

It should be emphasized that the therapeutic range in the present study applies only to VPB suppression, as there were no patients with atrial arrhythmias in the study group. In addition, the serum quinidine concentrations that were used to establish the therapeutic range were those associated with a definite drug response, even if the response was not considered optimal by the clinician treating the patient. Some patients with symptomatic ventricular tachycardia may require maximal tolerated doses of antiarrhythmic drugs with resultant high serum levels to prevent recurrences.²² Thus, we agree with Lown's group that the presence of a serum quinidine concentration that is within the therapeutic range should not deter the clinician from increasing the dose if necessary to gain better control of the arrhythmia.²³ This is illustrated by our patient H (Fig 1) in whom a drug response was not present at mean serum quinidine concentrations of 0.64 and 2.09 $\mu\text{g/ml}$, but was clearly evident when the dose was increased, resulting in a higher mean serum quinidine concentration of 3.50 $\mu\text{g/ml}$. A similar phenomenon has been reported by other investigators.^{1,11}

Conclusions

1 The range of serum quinidine levels at which a decrease in VPB frequency could be demonstrated in our patients was 0.72 to 5.92 $\mu\text{g/ml}$ using a specific HPLC quinidine assay.

2 Because of the variations that exist among individuals with arrhythmias, there is no optimal serum quinidine level at which maximal control of ventricular rhythm disturbances can be expected in all patients.

3 Although a significant correlation between serum quinidine level and VPB frequency cannot

Isovolumic relaxation period in man

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Early diastolic relaxation and compliance of the left ventricle the abnormal in many cardiac diseases. The rate of fall of left ventricular pressure, the rate of ventricular filling and the geometrical changes which occur in the left ventricle and its wall during early diastole have been studied in patients with coronary artery and other cardiac diseases¹⁻³ these measurements are useful but require invasive cardiac catheterization or computer processing of echocardiographic data.

The duration of the isovolumic relaxation period (IRP) is a simple parameter, but true IRP has been difficult to measure accurately^{4,5}. We have used echocardiography and phonocardiography to measure true IRP in normal subjects and in a large group of patients with different cardiac diseases to study its determinants and to evaluate its use as a simple noninvasive measurement of cardiac dynamics in terms of the present approach to ventricular relaxation and compliance.

Patients

Eighty three patients with different cardiac diseases were studied. They were divided into eight groups.

1 Normal subjects Ten patients were referred for echocardiography because of the presence of a soft systolic murmur. Their history, physical examination, electrocardiogram, chest x ray and

echocardiogram were normal and the diagnosis was that of an innocent systolic murmur.

2 Hypertension Fifteen patients had essential arterial hypertension with a diastolic blood pressure consistently above 90 mm Hg. Patients with known coronary artery disease (previous infarction, angina pectoris or diagnostic ischemic ECG changes) were not included in the group.

3 Coronary artery disease (CAD) Fifteen patients with coronary artery disease were studied. One patient had minor symptoms of an episode of myocardial infarction (NYHA Class 1) six were in Functional Class 2, five in Class 3 and three in Class 4 due to severe shortness of breath and left heart failure. The diagnosis of CAD was confirmed in all patients by cardiac catheterization and coronary angiography. In seven patients additional functional mitral incompetence was present and was confirmed by left ventriculography. Moderate or severe functional mitral incompetence was found in four and mild or trivial incompetence was seen in three.

4 Hypertrophic cardiomyopathy Nine patients had hypertrophic cardiomyopathy (HOCM). The diagnosis was made on the basis of physical examination and electrocardiogram and was confirmed by echocardiography.

5 Congestive cardiomyopathy (CMO) Seven patients presented with a large heart and severe cardiac failure. The etiology was viral myocarditis in three patients and daunorubicin toxicity in two. In the other two patients the etiology was uncertain but the disease probably followed a previous viral infection.

6 Aortic stenosis (AS) Four patients had severe aortic stenosis confirmed by cardiac catheterization. The peak systolic gradient across the aortic valve ranged from 70 to 110 mm Hg.

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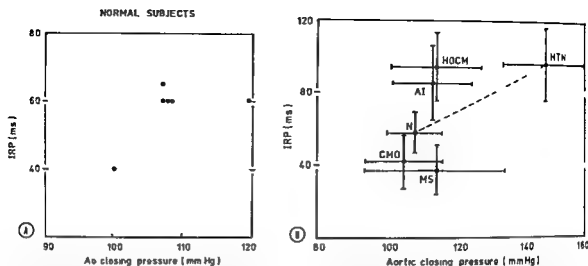


Fig 2 Relation between aortic closing pressure and isovolumic relaxation period (IRP) in normal subjects (A) ($r = 0.60$, $p < 0.05$) and in different cardiac diseases (B) IRP is prolonged in hypertrophic cardiomyopathy (HOCM) and in aortic incompetence (AI) and shortened in congestive cardiomyopathy (CMO) and mitral stenosis (MS)

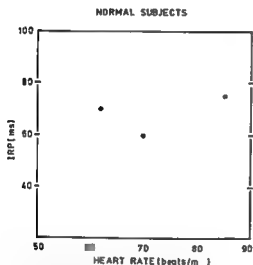


Fig 3 Relation between heart rate and isovolumic relaxation period (IRP) in normal subjects ($r = 0.50$, ns) IRP tended to increase with increasing heart rate

$$ICT \text{ (msec)} = PEP - (Q_{ECO} - C \text{ point}_{ECO})$$

The point of mitral leaflet coaption was not defined clearly in all patients ICT was not measured in patients in whom the quality of the recording was inadequate

8 Blood pressure The blood pressure (BP) was recorded with a baumanometer at the time the study was performed Aortic closing pressure (AoCP) was the systolic pressure minus one third the pulse pressure

Statistical analysis Comparison of the data between groups of patients was made using Stu-

dent's *t* test for unpaired data Correlation of data sets was sought using a least squares fit linear regression analysis Multiple regression analysis was used to derive an equation for predicted IRP in normal subjects

Results

The results are summarized in Tables I and II

IRP True IRP was 58 ± 11 msec in normal subjects It was prolonged in hypertension ($p < 0.001$), HOCM ($p < 0.001$), aortic stenosis ($p < 0.05$) and aortic incompetence ($p < 0.01$) and was shortened in congestive cardiomyopathy ($p < 0.05$) and in mitral stenosis ($p < 0.01$) In coronary artery disease IRP was normal or slightly increased (ns) The patients could be divided into two groups (Table III) six patients with CAD who had normal over all LV function ($\% \Delta S > 25\%$) had a prolonged IRP (80 ± 10 msec) ($p < 0.001$) while nine patients with decreased over all systolic function ($\% \Delta S \leq 25\%$) had a normal IRP (59 ± 30 msec)

Patients with CAD were also divided into three groups according to the duration of the IRP four patients had a shortened IRP (< 50 msec) (group 1) one patient had a normal IRP (50 to 60 msec) (group 2) and 10 had a prolonged IRP (> 60 msec or more) (group 3 Table III) All four patients in group 1 had extensive LV damage (global LV dysfunction on LV angiography) and all had moderate to severe additional functional

7 Aortic incompetence (AI) In 11 patients the diagnosis was aortic incompetence. Patients with additional mitral or other valve disease were not included in this group.

8 Mitral stenosis (MS) Twelve patients with pure mitral stenosis were studied. The diagnosis was made in nine patients by careful clinical examination, ECG, chest x-ray and echocardiography. In three patients cardiac catheterization was performed to exclude suspected disease of another valve. In the other patients the diagnosis was clear and we felt that it was not ethically justified to catheterize the patient.

Methods

Echocardiograms were recorded with an Ekoline 20A echocardiograph coupled to an Electronix for Medicine VR 6 or VR 12 photographic recorder. A 2.25 MHz focused transducer was used and recordings were made from the standard interspace along the left sternal border. M-mode sweeps were made in the long axis of the left ventricle and the remainder of the echocardiogram was recorded in standard fashion. A simultaneous phonocardiogram was recorded from the second and third left interspace or near the cardiac apex using an Electronics for Medicine piezoelectric crystal transducer. The aortic component of the second heart sound was clearly shown in all the tracings. A paper speed of 100 mm/sec was used to record time interval measurements.

The following measurements were made:

1 True isovolumic relaxation period (IRP) IRP was measured from the onset of the first high frequency deflection of the aortic component of the second heart sound on the phonocardiogram to the point of opening of the mitral leaflets on the echocardiogram. Only tracings in which the point of separation of the leaflets of the mitral valve was clearly visible were used in the study (Fig 1).

2 Anterior mitral leaflet (AML) opening time (DE time) The DE time was measured from the onset of mitral leaflet opening (point D) to the peak anterior open position (E point) of the anterior mitral leaflet.

3 Total time A-E point This was the sum of true IRP and the DE time. In patients with mitral stenosis the measurement corresponds to the A₂-opening snap time.

4 Mitral EF slope The steepest recorded

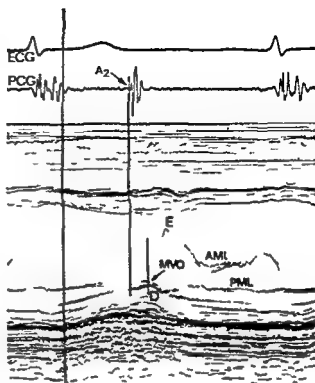


Fig 1 Electrocardiogram (ECG), phonocardiogram (PCG) and echocardiogram in a normal subject. Isovolumic relaxation period is the time interval between the onset of the high frequency component of the aortic component of the second heart sound (A₂) to the point of separation of the mitral leaflets (D point).

mitral EF slope was measured where possible where the EF slope was monophasic to avoid ambiguity in measurement.¹¹

5 PR AC time The time of closure of the AML (AC) was measured and subtracted from the PR interval of the electrocardiogram; this corrects for changes in the PR interval of the electrocardiogram.

6 LV dimensions and percentage shortening during systole Left ventricular diastolic diameter (Dd), systolic diameter (Ds) and the percentage shortening during systole (% ΔS) were measured in the standard plane of the M-mode echocardiographic sweep at the level of the edge of the mitral leaflets or their chordae tendineae.

7 Isovolumic contraction time (ICT) was measured by subtracting the time interval from the onset of the QRS complex of the electrocardiogram to the point of mitral coaptation on the echocardiogram (C point) from the pre-ejection period (PEP) (measured in standard fashion from a carotid pulse tracing).

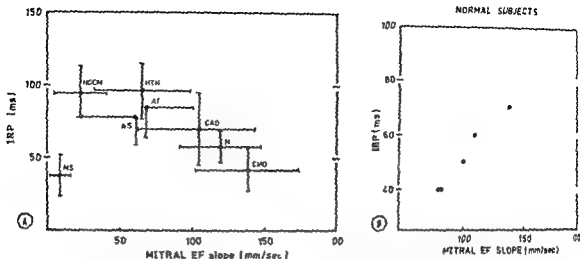


Fig 4 A Mitral EF slope and isovolumic relaxation period (IRP) in different cardiac diseases. IRP is prolonged in diseases associated with a reduced EF slope and short in congestive cardiomyopathy (CMO) where the EF slope is increased. In mitral stenosis (MS) both the EF slope and IRP are decreased. B IRP tends to increase with increasing EF slope in normal subjects ($r = 0.54$, ns).

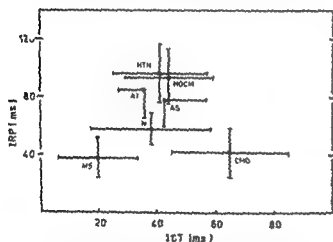


Fig 5 Isovolumic contraction time (ICT) and isovolumic relaxation time (IRP) in different cardiac diseases. In mitral stenosis (MS) both ICT and IRP are reduced while in congestive cardiomyopathy (CMO) ICT is prolonged and IRP is shortened. In aortic incompetence (AI), aortic stenosis (AS), hypertrophic cardiomyopathy (HOCM) and hypertension (HTN) IRP is prolonged with no change or with a small increase in ICT.

heart rate. IRP was related to aortic closing pressure in normal subjects ($r = 0.65$, $p < 0.05$) (Fig 2) and increased in patients with systemic hypertension. Patients with HOCM and aortic incompetence fell upwards and to the left on the graph (Fig 2) indicating prolongation of the IRP for any given BP. Patients with MS and CMO had a short IRP for their blood pressure.

IRP increased slightly with increasing heart rate in normal subjects ($r = 0.50$, ns) (Fig 3) one patient disturbed the statistical relationship.

Multiple regression analysis correlating IRP with aortic closing pressure (AoCP) and heart rate (HR) in normal subjects greatly improved the correlation coefficient ($R = 0.80$, $p < 0.05$) compared with the correlation coefficients for each of these variables taken independently and provided the following equation for predicted IRP:

$$\text{IRP} = 0.97 \text{ AoCP} + 0.62 \text{ HR} - 56.6$$

Using this equation the deviation of the measured IRP from predicted normal (ΔIRP) was calculated in each patient. The mean ΔIRP for each patient group is given in Table I. Measured IRP was prolonged in HOCM and AI ($+\Delta\text{IRP}$) and was short in CMO and MS ($-\Delta\text{IRP}$) and normal in hypertension and CAD although there was considerable individual variation in each group so that the standard deviations were high.

DE time. The DE time measured 58 ± 17 msec in normal subjects. It was normal in hypertension in CAD (all groups) in CMO, AS and AI and was prolonged in HOCM ($p < 0.05$) and was shortened in MS ($p < 0.01$).

A-E point. The duration A-E point was 116 ± 13 msec in normal subjects (Table II). It was prolonged in hypertension ($p < 0.01$), aortic stenosis (ns) and aortic incompetence ($p < 0.05$) and was greatly increased in HOCM ($p < 0.01$). In CAD the A-E point time was increased especially in patients with normal systolic function ($\% \text{ AS} > 25\%$) ($p < 0.001$). The A-F point time was slightly shortened in CMO (ns) and was greatly shortened in MS ($p < 0.001$). There was

Table I Echocardiographic measurements in diastole

| | No | True IRP msec | DE time msec | A E point msec | Mitral EF slope mm/sec | PR-AC msec |
|-----------------------------|----|------------------|-----------------|-------------------|------------------------------|---------------|
| Normal subjects | 10 | 58 ± 11 | 58 ± 12 | 116 ± 13 | 119 ± 29 | 70 ± 7 |
| Hypertension | 15 | 96 ± 20 | 55 ± 18 | 151 ± 32 | 60 ± 34 | 58 ± 18 |
| Coronary artery disease | 15 | 69 ± 17 | 59 ± 20 | 128 ± 36 | 104 ± 40 | 41 ± 24 |
| Hypertrophic cardiomyopathy | 9 | 94 ± 10 | 72 ± 14 | 167 ± 25 | 23 ± 19 | 69 ± 14 |
| Congestive cardiomyopathy | 7 | 42 ± 11 | 59 ± 21 | 101 ± 30 | 138 ± 36 | 54 ± 32 |
| Aortic stenosis | 4 | 78 ± 21 | 64 ± 41 | 141 ± 52 | 61 ± 45 | 70 ± 27 |
| Aortic incompetence | 11 | 85 ± 22 | 54 ± 12 | 139 ± 20 | 68 ± 32 | 73 ± 30 |
| Mitral stenosis | 19 | 38 ± 14 | 40 ± 15 | 77 ± 90 | 9 ± 7 | — |

See text for details of indices and abbreviations

p < 0.05

p < 0.01

p < 0.001

Table II Measurements of systolic LV function

| | LVDd cm. | LVDs cm. | % AS | ICT msec | Ao closing pressure mm Hg | Heart rate beats/min |
|-----------------------------|-------------|-------------|---------|-------------|---------------------------------|-------------------------|
| Normal subjects | 50 ± 0.3 | 32 ± 0.2 | 37 ± 4 | 111 ± 27 | 107 ± 8 | 67 ± 10 |
| Hypertension | 45 ± 0.7 | 28 ± 0.7 | 38 ± 11 | 41 ± 16 | 146 ± 18 | 74 ± 10 |
| Coronary artery disease | 59 ± 0.9 | 45 ± 1.2 | 24 ± 11 | 36 ± 19 | 116 ± 13 | 87 ± 14 |
| Hypertrophic cardiomyopathy | 44 ± 0.6 | 32 ± 0.4 | 49 ± 6 | 44 ± 15 | 113 ± 13 | 68 ± 14 |
| Congestive cardiomyopathy | 68 ± 1.2 | 58 ± 1.1 | 16 ± 7 | 65 ± 20 | 105 ± 11 | 100 ± 11 |
| Aortic stenosis | 46 ± 0.4 | 30 ± 1.0 | 34 ± 15 | 42 ± 15 | — | 65 ± 4 |
| Aortic incompetence | 63 ± 0.6 | 42 ± 0.7 | 33 ± 7 | 36 ± 11 | 112 ± 11 | 60 ± 16 |
| Mitral stenosis | 47 ± 0.8 | 31 ± 0.6 | 36 ± 3 | 20 ± 14 | 117 ± 21 | 76 ± 14 |

See text for details of indices and abbreviations

p < 0.05

p < 0.01

p < 0.001

mitral incompetence Group 1 echocardiograms showed great LV enlargement (Dd 63 ± 0.6 p < 0.001) and a low % AS (p < 0.001). Sinus tachycardia was present. The single patient in group 2 (normal IRP) also had severe left ventricular enlargement and LV dysfunction but was hypertensive; this may have increased his IRP so that it was not shortened as in the other patients with severe LV dilatation and LV dysfunction. In contrast patients in group 3 (prolonged IRP) had

mild LV enlargement (Dd 56 ± 0.4 p > 0.05) and a slightly decreased LV shortening fraction (mean % AS 27 ± 12 p < 0.05) although eight patients in group 3 had suffered previous infarction with regional ventricular asynergy and three had mild or trivial functional mitral incompetence. LV end diastolic pressure (25 ± 10 mm Hg) was increased less than in group 1 (40 ± 6 mm Hg).

Relation of IRP to systemic blood pressure and

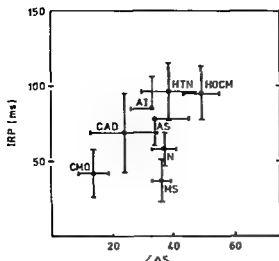


Fig 3 Systolic shortening fraction (% ΔS) and isovolumic relaxation period (IRP) in normal subjects (N) and in different cardiac diseases. % ΔS and IRP increased or decreased in parallel, except in mitral stenosis (MS) where IRP was markedly shortened.

different cardiac diseases are shown in Fig 5. In hypertension, HOCM, AI, and AS, IRP increased with no or little change in ICT. In MS, both IRP and ICT were short, while in CMO, IRP was short and ICT was prolonged.

2 LV shortening fraction (% ΔS) IRP was related to percentage shortening of the LV in systole (Fig 6). In general, in diseases where % ΔS was high, IRP was prolonged; patients who had a lower % ΔS had a shorter IRP. In MS, IRP was short for the % ΔS .

Discussion

Echocardiography permits accurate measurement of the true isovolumic relaxation period of the left ventricle. Our values for IRP (58 ± 11 msec) are shorter than those of most previous studies which used older methods to mark the end of the IRP: invasive cardiac catheterization,⁴ angiographic studies of the O point of the apexcardiogram,¹ and phono Doppler measurements.¹¹ A previous echocardiographic study used the onset of rapid opening of the anterior mitral leaflet to mark the end of the IRP.¹² We measured IRP from aortic closure to the point of separation of the mitral leaflets on the echocardiogram; we believe that the point of separation of the leaflets is less ambiguous and conceptually more correct as a marker of the end of the true IRP. Echocardiography also permits measurement of the mitral valve opening time (DE) and the time A_2 —maximum mitral opening (E point).¹³ A

Table IV Deviation of IRP from predicted normal values in cardiac disease (msec)

| | | |
|-----------------------------|-----|----|
| Normal subjects | 0 | 6 |
| Hypertension | -3 | 4 |
| Hypertrophic cardiomyopathy | +3 | 29 |
| Congestive cardiomyopathy | -37 | 31 |
| Aortic incompetence | +31 | 47 |
| Mitral stenosis | -31 | 41 |
| Coronary artery disease | | |
| — % $\Delta S > 25\%$ | +3 | 5 |
| — % $\Delta S \leq 25\%$ | -5 | 29 |

Mean \pm SD

measurement previously possible only in patients with mitral stenosis and an opening snap or with a prosthetic mitral valve producing an audible opening click.

Isovolumic relaxation period is the time interval from aortic valve closure to mitral opening and depends on the aortic closing pressure, the height of the v wave in the left atrium (mitral opening pressure), and the rate of pressure fall in the left ventricle (Fig 7). IRP may also be heart rate dependent and tends to increase in normal subjects with increasing heart rate. In contrast to previous work using older methods for measuring IRP,¹⁴ our study shows an important relation to systemic blood pressure. In normal subjects, a use of the multiple regression analysis (corrected for heart rate and blood pressure) improved the relationship significantly. Multiple regression analysis provided us with an equation for predicting IRP which may be useful in assessing isovolumic relaxation time in cardiac disease. We did not measure left atrial pressure, but IRP is very short in mitral stenosis and especially short in patients with CAD and important additional functional mitral incompetence. The rate of LV pressure fall in early diastole (i.e., early diastolic relaxation of the LV) is also a determinant of IRP; the greatly increased IRP and ΔIRP observed in patients with HOCM and the increase in IRP in patients with AS may be due to this mechanism, since both diseases are associated with high LV chamber stiffness as a consequence of severe LVH.^{15,16} In systemic hypertension, the long IRP is probably the result of the increased aortic pressure; in most patients, the mean ΔIRP is normal, in some patients there may also be a change in LV chamber compliance due to ventricular hypertrophy. Systemic blood pres-

Table III Echocardiographic measurements in patients with coronary artery disease

| HR beats/ min | True IRP msec | DE time msec | A E point msec | EF slope mm /sec | PR-AC msec | ICT msec | LVDd cm | LVDs cm | AS | Ao closing pressure mm Hg |
|--|---------------------|--------------------|----------------------|------------------------|---------------|-------------|------------|------------|---------|------------------------------------|
| <i>a According to systolic shortening fraction</i> | | | | | | | | | | |
| Group 1 (% ΔS > 25%) n = 6 75 ± 12 | 85 ± 10 | 65 ± 15 | 150 ± 20 | 84 ± 31 | 65 ± 7 | 37 ± 28 | 5.3 ± 0.5 | 3.4 ± 0.5 | 36 ± 6 | 113 ± 6 |
| Group 2 (% ΔS ≤ 25%) n = 9 94 ± 10 | 81 ± 30 | 56 ± 23 | 114 ± 37 | 117 ± 47 | 36 ± 22 | 35 ± 15 | 6.3 ± 0.8 | 5.3 ± 0.9 | 17 ± 7 | 118 ± 16 |
| <i>b According to duration of IRP</i> | | | | | | | | | | |
| Group 1 (Short IRP) n = 4 108 ± 6 | 33 ± 22 | 58 ± 22 | 90 ± 27 | 114 ± 52 | 46 ± 7 | 45 ± 1 | 6.3 ± 0.6 | 5.0 ± 0.6 | 21 ± 6 | 108 ± 5 |
| Group 2 (No normal IRP) n = 1 87 | 60 | 50 | 110 | 143 | 70 | — | 8.0 | 6.9 | 14 | 133 |
| Group 3 (Pro longed IRP) n = 10 81 ± 12 | 110 ± 10 | 61 ± 21 | 146 ± 28 | 96 ± 37 | 41 ± 22 | 30 ± 22 | 5.6 ± 0.4 | 4.1 ± 1.1 | 27 ± 12 | 116 ± 13 |

See text for details of indices and abbreviations

p < 0.05
p < 0.01
p < 0.001 } Compared to the normal group

an over all linear relationship between IRP and A-E ($r = 0.87$ $p < 0.001$)

Other echocardiographic measurements related to LV compliance. The mitral EF slope was decreased in hypertension ($p < 0.001$) aortic stenosis ($p < 0.05$) and aortic incompetence ($p < 0.01$) and was greatly decreased in HOCM ($p < 0.001$). It was also decreased ($p < 0.05$) in the six patients with CAD who had normal LV function (% ΔS > 25%) but was not different from normal when the whole CAD group was examined together. The EF slope tended to increase in CMO although the difference was not statistically significant. The inverse relation between IRP and the mitral EF slope in different diseases is shown in Fig 4A. Diseases associated with a prolonged IRP had a reduced mitral EF slope. In CMO IRP was short and the EF slope increased. In MS both IRP and the mitral EF slope were very short. The relation between IRP

and EF slope tended to be positive however within the group of normal subjects (Fig 4B) and was positive or unrelated within the other disease states.

The PR-AC time was 70 ± 7 msec in normal subjects. It was normal in AS, AI and HOCM and slightly decreased in hypertension (ns). The PR-AC time was short in the nine patients with CAD who had a decreased shortening fraction ($p < 0.001$). There was no relation between the PR-AC time and IRP.

Relation between IRP and measurements of systolic LV performance

1 Isovolumic contraction time (ICT) was 38 ± 22 msec in normal subjects. It was shortened in AI and MS and increased in CMO. The differences did not reach statistical significance because the number of patients in which the measurement could be made accurately was small. The mean values for ICT and IRP in

Other simple echocardiographic measurements which have been related to LV compliance include the mitral EF slope and the PR-AC time. The mitral EF slope is related to early diastolic filling and in the absence of mitral stenosis to early diastolic compliance.² IRP and the A-E point time measure a similar phenomenon to the EF slope—the rate of LV relaxation and filling in early diastole—and were related to the mitral EF slope. The three measurements do not examine precisely the same period in diastole; however, studies of LV relaxation and compliance should define very carefully the exact period of diastole to which they refer since the diastolic pressure, volume, and stress-strain relations change throughout diastole.⁴ The PR-AC time is a very rough and not constant measurement of end-diastolic compliance. A long AC time (short PR-AC) indicating a high LV end diastolic pressure,⁷ there was no relation between the PR-AC time and true IRP which measures LV function in early diastole.

There was a positive relationship between systolic LV shortening ($\% \Delta S$) and the duration of the IRP in different cardiac diseases. In HOCM $\% \Delta S$ was increased and IRP greatly prolonged while in CMO $\% \Delta S$ was reduced and IRP was short. Patients with increased contractility may have an increased intracellular Ca^{2+} and this may prolong early diastolic relaxation, an active process dependent on the Ca^{2+} reuptake mechanisms. Increased systolic tension may therefore be associated with greater residual tension during early diastole and a prolonged IRP. We did not make serial studies of the effects of positive and negative inotropic intervention in the same patients; however, and can provide no further information relating to these changes. Similarly, the relationship between ICT and IRP was not clear in our study, although hemodynamic studies have shown that peak negative dp/dt is related to peak positive dp/dt .

Summary

Isovolumic relaxation period (IRP) was measured noninvasively from the onset of the aortic component of the second heart sound on the phonocardiogram to the point of separation of the mitral leaflets on the echocardiogram. IRP was measured in 83 patients: 10 normal subjects and 73 patients with different cardiac diseases.

The duration of IRP was 0.8 ± 0.11 msec in normal subjects. It was prolonged in hypertension ($p < 0.001$), HOCM ($p < 0.001$), aortic stenosis ($p < 0.05$), and aortic incompetence ($p < 0.01$), and was shortened in congestive cardiomyopathy ($p < 0.05$) and mitral stenosis ($p < 0.01$). In patients with coronary artery disease and normal over all systolic LV function, IRP was prolonged ($p < 0.001$). IRP was prolonged in four patients with coronary disease who had severe LV dysfunction and severe additional mitral incompetence.

IRP was related to systemic blood pressure, percentage shortening of the LV in systole, and the mitral EF slope. It tended to increase with increasing heart rate and a regression equation was developed for predicting IRP in relation to blood pressure and heart rate in normal subjects. There was no relation to the PR-AC time or to isovolumic contraction time. IRP is a useful measurement of LV dynamics in early diastole.

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sure and heart rate are easy to measure at the bedside however and can be taken into account when assessing measurements of IRP in different cardiac diseases

IRP is prolonged in most patients with coronary artery disease especially in those in whom over all LV contraction as measured by $\% \Delta S$ is normal IRP was prolonged in all but one patient but mean ΔIRP was essentially normal since one patient in the group had a very low ΔIRP (-48 msec) These data confirm previous studies^{9,11} and probably correspond to the decreased peak negative dp/dt in patients with myocardial ischemia¹ The increased IRP may also be related to asynchronous relaxation of different regions of the myocardium³ (Fig 7) It is interesting that patients with severe extensive LV dysfunction and functional mitral incompetence have a short IRP Mean ΔIRP was again almost normal since one patient had a prolonged corrected IRP but ΔIRP was short in the other patients in the subset confirming a real shortening of the duration of isovolumic relaxation The findings in these patients are similar to those of congestive cardiomyopathy where the large dilated left ventricle may have increased operative chamber compliance at operative volume in early diastole The rapid mitral EF slope supports this concept although a high LA pressure and high LA v wave may contribute to the shortened IRP in patients with severe LV dysfunction and important functional mitral incompetence

Aortic incompetence was associated with a prolonged IRP and ΔIRP There is no true isovolumic relaxation period in aortic incompetence and ventricular filling commences immediately with the onset of ventricular relaxation retrograde ventricular fill may delay the onset of mitral valve opening although there may also be a decrease in LV chamber compliance because of ventricular hypertrophy and volume overload which further prolongs measured IRP

The DE time was normal in all groups of patients except those with HOCM who had a prolonged DE time and the A_2 -E point time which increased in general in parallel with the increase in true IRP was longest in patients with HOCM The great increase in DE time in HOCM may be related to the severe LVH and decreased chamber compliance which occurs in severe LV hypertrophy It is noteworthy that the DE time was not prolonged in hypertension emphasizing

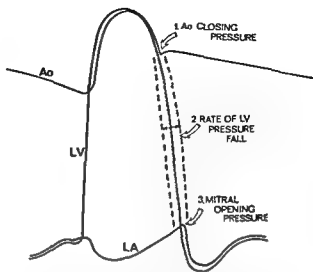


Fig 7 Diagrammatic left ventricular (LV), aortic (Ao) and left atrial (LA) pressure pulse tracings Isovolumic relaxation period (IRP) depends on (1) aortic closing pressure (2) rate of fall of LV pressure and (3) mitral opening pressure The rate of fall of LV pressure may be the resultant of regional asynchrony in ventricular relaxation in patients with cardiac diseases

again the importance of the high aortic pressure rather than the LV hypertrophy in the prolongation of IRP in hypertensive patients The mean DE time was also not prolonged in coronary artery disease It seems that changes in regional muscle stiffness due to fibrosis (CAD) or mild to moderate LVH and moderate changes in LV chamber stiffness (hypertension AS) are not sufficient to affect mitral valve opening once this has started it is only in patients with severely abnormal chamber stiffness due to unusual LV hypertrophy and geometrical changes within the ventricle (e.g. HOCM) that there is prolongation of the mitral valve opening time DE

The study also provides information in relation to the A_2 -E point (A -OS time) in normal subjects and in patients with mitral stenosis¹² Measurement of true IRP is a better measure of the severity of MS than total time A_2 -OS since mitral valve thickening and rigidity may prolong the DE time in some patients with severe MS to offset the extreme shortening of true IRP in patients with severe disease The normal A -E point time = 116 ± 13 msec There is a decrease in A -OS time in MS but we did not subdivide patients with MS further since not all patients with mitral stenosis underwent cardiac catheterization

The relationship of pulmonary artery wedge pressure to the posterior aortic wall echocardiogram in patients free of obstructive mitral valve disease

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Numerous investigations have been designed to uncover reliable echocardiographic measurements which reflect human left ventricular compliance. Since decreased left ventricular compliance will be reflected in an increased left ventricular filling or pulmonary artery wedge pressure, a noninvasive method to assess this pressure would have widespread clinical utility.

Based upon echocardiographic measurements it has been proposed that characteristic aortic wall motion represents left atrial filling and emptying events.¹ Resistance to left atrial emptying was estimated by Strunk and colleagues using the fraction of passive posterior aortic wall motion occurring in the first third of diastole (atrial emptying index AEI). In that study patients had fixed mitral valve obstruction as the cause of prolonged left atrial emptying.

The purpose of this study was to evaluate the relationship of this index (AEI) to left ventricular filling pressures in patients free of mitral valve obstruction which in such patients is primarily related to differences in left ventricular compliance.

Materials and methods

Twenty five consecutive unselected patients requiring hemodynamic evaluation had M mode

echocardiography performed at the time of left ventricular filling pressure (pulmonary capillary wedge) measurement. Data from six patients were rejected: four because of suboptimal echocardiograms and two because of evidence of mitral stenosis. Two patients were studied twice, one after a change in heart rhythm and the other after treatment with vasodilators for a total of 27 studies in 19 patients. Studies were performed after informed consent was obtained. There were eight women and 11 men with a mean age of 53 years (range 30 to 74 years). The final diagnosis was coronary artery disease in 14 patients, congestive cardiomyopathy in two, and three patients were judged to be normal.

Echocardiograms were made using a 2.25 MHz transducer placed along the left sternal border in the third or fourth intercostal space and rotated until elements of aortic leaflets were seen within the aortic root. The image of the aortic root was expanded to the maximum recording scale in order to facilitate measurements. All aortic measurements were made in that part of the recording showing maximal total aortic root excursion.

The method described by Strunk and associates¹ and by Lewis and colleagues² for determining the atrial emptying index was employed. For patients in sinus rhythm, posterior aortic wall motion reflecting passive left ventricular filling is from points O to A (Fig 1). The point where the posterior aortic wall begins its posterior motion is O, and the A point describes a second abrupt posterior movement caused by atrial contraction. The left atrial emptying index (X/OA) is the ratio of the posterior aortic wall motion occurring in

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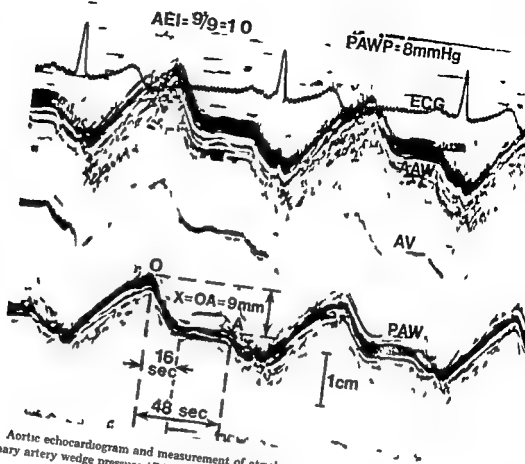


Fig 2 Aortic echocardiogram and measurement of atrial emptying index (AEI) from a patient with a normal pulmonary artery wedge pressure (PAWP). Abbreviations same as in Fig 1

Table I Summary of data

| Case No | Age (yr) | Sex | Diagnosis | Rate rhythm | TAE (mm) | AEI | PAWP (mm Hg) |
|---------------------------|----------|-----|-----------|-------------|----------|------|--------------|
| Group A (PAWP ≤ 12 mm Hg) | | | | | | | |
| 1 | 45 | M | CAD | 107 S | 71 | 0.88 | 8 |
| 2 | 74 | P | CAD | 60 J | 50 | 1.00 | 9 |
| 3 | 64 | M | CAD | 60 S | 76 | 0.87 | 5 |
| 4 | 62 | M | CAD | 67 S | 105 | 1.00 | 5 |
| 5 | 54 | M | CAD | 68 S | 90 | 0.93 | 9 |
| 6 | 30 | M | CAD | 78 S | 90 | 1.00 | 7 |
| 7 | 42 | M | N | 79 S | 112 | 1.00 | 8 |
| 8 | 47 | M | CAD | 73 S | 107 | 0.91 | 4 |
| 9 | 51 | F | N | 80 S | 100 | 0.88 | 6 |
| 10 | 42 | F | CAD | 65 S | 108 | 1.00 | 8 |
| 11 | 53 | M | N | 77 S | 91 | 0.90 | 6 |
| 12 | 53 | M | CAD | 74 S | 107 | 0.93 | 8 |
| Group B (PAWP > 12 mm Hg) | | | | | | | |
| 1 | 40 | M | CM | 102 S | 50 | 0.63 | 22 |
| 2 | 53 | F | CAD | 72 S | 64 | 0.64 | 25 |
| 3 | 44 | F | CM | 115 J | 89 | 0.43 | 37 |
| 4 | 41 | F | CM | 91 S | 100 | 0.40 | 77 |
| 5 | 58 | F | CAD | 101 S | 35 | 0.36 | 35 |
| 6 | 64 | F | CAD | 83 AF | 81 | 0.56 | 22 |
| 7 | 70 | F | CAD | 81 S | 40 | 1.00 | 15 |
| 8 | 54 | M | CAD | 84 AF | 42 | 0.66 | 19 |
| 9 | 54 | M | CAD | 72 AF | 40 | 0.78 | 15 |

Abbreviations AEI = atrial emptying index AF = atrial fibrillation CAD = coronary artery disease CM = cardiomyopathy J = junctional rhythm N = normal PAWP = pulmonary artery wedge pressure S = sinus rhythm TAE = total aortic excursion

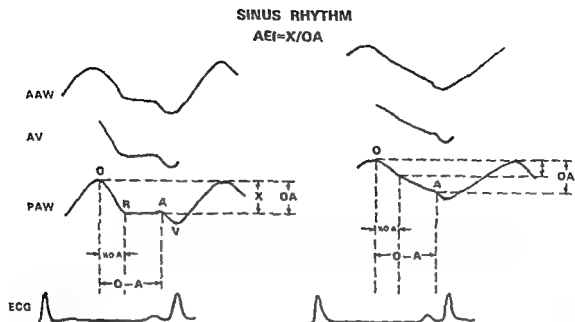


Fig 1 Schematic drawing illustrating the calculation of the atrial emptying index (AEI) for patients in sinus rhythm Left $AEI = X/OA = 1.0$ Right $AEI = X/OA < 1.0$ Passive atrial emptying occurs between points O and A Abbreviations AAW = anterior aortic wall AV = aortic valve PAW = posterior aortic wall

the first third of this passive emptying period (X) to the total passive emptying (OA) For patients in atrial fibrillation the end of the passive diastole is taken as the onset of ventricular systole Point V on the posterior aortic wall echocardiogram corresponds to the end of the QRS complex on the electrocardiogram The atrial emptying index is again the ratio of the motion occurring during the first third of this period (X) to the total passive emptying (OV)

The anterior posterior excursion of the aortic root was measured using only the leading edge of the posterior aortic wall echo and averaged over five cycles Linear regression equations and correlation coefficients were calculated and group comparisons were made using Student's unpaired t test

Results

There were 12 patients with normal hemodynamics (group A filling pressure ≤ 12 mm Hg), and seven patients (nine studies) with abnormal hemodynamics (group B filling pressure > 12 mm Hg) (Table I) Of the 12 patients in group A 11 were in sinus rhythm and one in a junctional rhythm For group B four were in sinus rhythm two in atrial fibrillation (one studied twice) and

one patient was studied first in a junctional rhythm and then after conversion to sinus rhythm The mean pulmonary wedge pressures for groups A and B were 69 ± 17 mm Hg (mean \pm SD) and 236 ± 69 mm Hg respectively ($p < 0.01$)

Figs 2 and 3 demonstrate normal and abnormal AEIs respectively The mean atrial emptying index for Group A was 0.94 ± 0.06 and for group B it was 0.61 ± 0.02 ($p < 0.001$) (Fig 4) There was a significant ($p < 0.001$) negative correlation between pulmonary artery wedge pressure and the AEI $r = -0.91$ Mean heart rate for group A was 74 beats/minute compared to 89 beats/minute in group B ($p < 0.05$) Because of the potential influence of heart rate on the left atrial emptying pattern and because of the differences in heart rate in our two groups we investigated the possibility that the differences observed in the AEI were secondary only to rate Normalization for heart rate was accomplished by dividing the AEI by \sqrt{RR} A significant ($p < 0.001$) correlation remained with an r value of -0.85 (Fig 5)

No patient in the normal group had an atrial emptying index below 0.80 and no patient in group B with a pulmonary wedge pressure greater

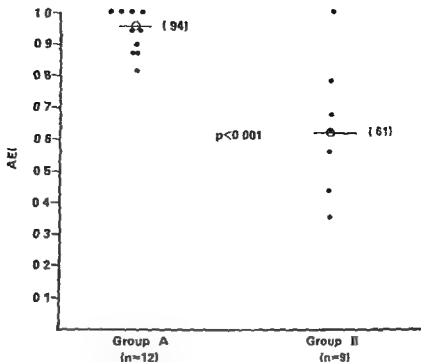


Fig 4 The atrial emptying index (AEI) in patients with normal (group A PAWP ≤ 12 mm Hg) and abnormal (group B PAWP > 12 mm Hg) pulmonary artery wedge pressures P = probability

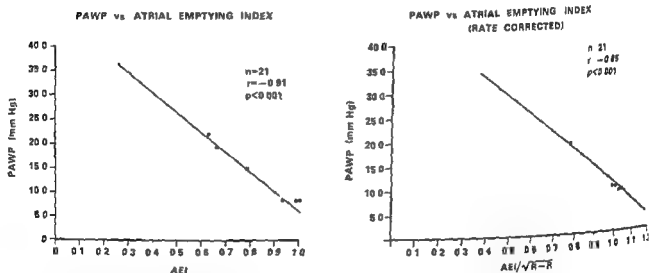


Fig 5 Pulmonary artery wedge pressure (PAWP) plotted against the atrial emptying index (AEI) Left before and right after rate correction. There is a high degree of negative correlation both before ($r = -0.91$) and after ($r = -0.85$) rate correction p = probability

root excursion in patients with valvular heart disease and found a statistically significant decrease in motion in patients with mitral stenosis and a statistically significant increase in motion in patients with mitral regurgitation as compared to a normal population. They found no significant difference in patients with aortic regurgitation as compared to the normal popula-

tion. We did not include data from patients with significant valvular disease but recognize the possibility that markedly increased aortic compliance or altered left atrial filling and emptying secondary to severe mitral regurgitation may alter these correlations.

Total anteroposterior aortic root motion or total aortic root excursion (TAE) has correlated

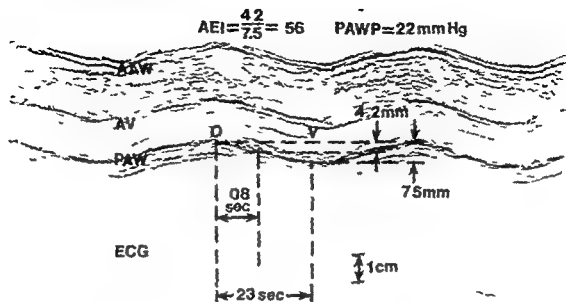


Fig. 3 Aortic echocardiogram and measurement of atrial emptying index (AEI) from a patient with an elevated pulmonary artery wedge pressure (PAWP). Abbreviations same as in Fig. 1

than 18 mm Hg had an atrial emptying index greater than 0.66

The total aortic root excursion for groups A and B were 92 ± 19 mm and 60 ± 24 mm ($p < 0.01$) respectively. When the total aortic root excursion was related to the pulmonary wedge pressure for the total population there was a very weak correlation with an r value of -0.46 ($p < 0.04$) which did not improve after normalizing for rate.

Discussion

Previous attempts to establish echocardiographic determinants of left ventricular pressure and compliance have concentrated on the mitral valve echocardiogram. Konecke and co-workers⁸ reported that the echocardiographic pattern of mitral valve motion is altered in patients with markedly elevated left ventricular end diastolic pressure. They found that a PR AC interval of 0.06 sec or less as derived from the electrocardiogram and mitral valve echocardiogram correlated with an elevated left ventricular end diastolic pressure (≥ 20 mm Hg) when the atrial component of the left ventricular pressure pulse is at least 8 mm Hg. A recent report by Lewis and co-workers⁹ did not substantiate the reliability of this measurement either in the resting or the dynamic state.

It has been suggested that the mitral E-F slope may be a function of left ventricular compliance.¹⁰ A decrease in the diastolic closure rate

of the mitral valve, a constant finding in mitral stenosis, has also been reported in conditions without mitral valve pathology but with impaired left ventricular filling.¹¹ DeMaria and co-workers established a correlation between transmitral flow in the first third of diastole and the E-F slope ($r = 0.87$) and although the mitral E-F slope did not correlate closely with compliance they found that ventricular compliance was generally reduced in patients with an early mitral diastolic closing velocity of less than 75 mm/second. Vignola and associates¹² demonstrated that the pressure/volume relationship in the left ventricle in early diastole is an important determinant of the mitral E-F slope.

Although the echocardiographically observed aortic root motion may be the result of many factors including aortic compliance, Strunk and co-workers¹³ and Akgun and colleagues¹⁴ presented data supporting the hypothesis that aortic wall motion is governed mainly by the rate of left atrial volume changes. The posteriorly directed aortic wall motion during ventricular diastole would then be secondary to the rate of left atrial emptying. Mechanical obstruction to flow of blood at the level of the mitral valve alters the pattern of left atrial emptying and Strunk and co-workers¹³ quantified the degree of obstruction with the echocardiographically measured atrial emptying index.

Akgun and associates¹⁴ also compared aortic

Ischemic cardiomyopathy A clinicopathologic study of fourteen patients

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A cardiomyopathy due to coronary artery disease is a relatively new concept first proposed in 1969.¹ In 1970 Burch and co workers² coined the term ischemic cardiomyopathy for those patients with coronary artery disease enlarged hearts and the clinical manifestations of a congestive cardiomyopathy. Since that time further information has been obtained from natural history^{3,4} and cardiac catheterization⁵ studies of patients with ischemic cardiomyopathy. The term ischemic cardiomyopathy has been broadened by some to include any patient with coronary disease and a decreased left ventricular ejection fraction regardless of symptoms or heart size.⁶ In order to define a morphological explanation for ischemic cardiomyopathy we studied 14 autopsied patients who met the clinical criteria for ischemic cardiomyopathy. At autopsy these patients had severe coronary artery disease with injury in multiple vascular distributions. Although the hearts were dilated and hypertrophied the myocardial walls were disproportionately thinned suggesting inadequate myocardial thickness for the degree of dilatation. The latter may be a factor contributing to the diffuse inadequacy of myocardial function in a disease of regional injury.

Materials and methods

Patients from the autopsy files of The Johns Hopkins Hospital were included in this study if

they met the clinical definition of this entity including significant (> 75%) coronary narrowing in at least one vessel a longstanding clinical history of congestive heart failure cardiomegaly and if the hearts had been routinely processed at autopsy with postmortem coronary arteriography and fixation of the heart in formalin in an undistended state. Patients were excluded if (1) there was a history of hypertension or alcohol abuse (2) there was evidence of primary valvular disease congenital heart disease or ventricular aneurysm formation or (3) there was evidence of other etiologies of cardiomyopathy (sarcoid amyloid hypertrophic cardiomyopathy etc). Over 200 consecutive autopsy cases with coronary artery disease whose hearts had been similarly processed at autopsy were reviewed and 14 met the above clinical criteria for inclusion in the study. The patient's clinical records were studied and coronary risk factors electrocardiograms and chest radiographs were reviewed and tabulated.

At autopsy all hearts were prepared by postmortem angiography utilizing injection of a gelatin pigment barium mass at pressures of 100 to 150 mm Hg controlled by manometer and subsequently fixed in formalin in a distended state. Sets of stereoscopic radiographs were prepared of the intact heart and its transverse sections. The hearts were studied grossly and histologically for the presence of myocardial lesions and obstructive disease of the coronary arteries. The hearts were serially sliced and transverse sections were subjected to planimetry denoting areas of recent and recent myocardial necrosis. Each transverse slice was weighed minus the right ventricle (using a digitizing computer (Hewlett Packard) the grams of infarcted tissue and the percent of left ventricle infarcted was obtained.

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with stroke volume or stroke index¹⁴ but has not been characterized as a function of left ventricular diastolic hemodynamics. Burggraf and colleagues² looking at total aortic root systolic anteroposterior motion found that a value < 7 mm indicated poor left ventricular performance although they did not find it to be a predictor of abnormal left ventricular end diastolic pressure. We found only a very weak correlation between total aortic root excursion and mean pulmonary artery wedge pressure but the mean total excursion for those patients with pulmonary wedge pressures > 12 mm Hg was 60 ± 24 mm. Although there was considerable overlap of values this was significantly ($p < 0.01$) lower than those patients with wedge pressures ≤ 12 mm Hg whose excursion was 92 ± 19 mm.

The results of this study indicate that the atrial emptying index provides a noninvasive measure of left ventricular filling pressures in a diverse group of patients. This relationship is not limited to patients with obstructive mitral valve disease and therefore may have more general clinical utility.

Summary

Aortic wall echocardiograms were obtained simultaneously with pulmonary artery wedge pressures (PAWP) in 21 patients free of obstructive mitral valve disease. There was a significant ($p < 0.001$) negative correlation between the fraction of passive posterior aortic wall motion occurring in the first third of diastole (the atrial emptying index—AEI) and the pulmonary artery wedge pressure ($r = -0.91$). The AEI for patients with normal PAWP (≤ 12 mm Hg) was 0.94 ± 0.06 (mean \pm SD) compared with 0.61 ± 0.20 for those with abnormal PAWP (> 12 mm Hg). No patient with a normal PAWP had an AEI < 0.80 and no patient with a PAWP > 18 mm Hg had an AEI > 0.66 . These data suggest that analogous to the reported use of the AEI to estimate severity of mitral obstruction the index provides a noninvasive measure of left ventricular filling pressure when the mitral valve is normal.

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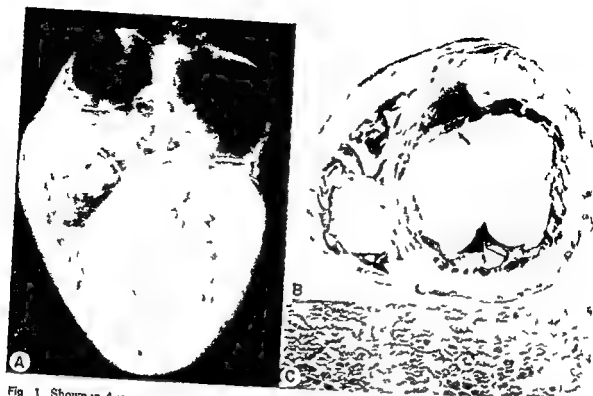


Fig 1 Shown in A is a postmortem angiogram of a patient with ischemic cardiomyopathy. The heart is diffusely dilated, the walls are thinned, and severe coronary occlusive disease is present. A transverse section through both right and left ventricles is shown in B. Subendocardial infarcts are present anteriorly, laterally, posteriorly, and a transmural infarct is present in the septum. A mural thrombus overlays the anteroseptal infarct (arrow). All infarcts were healed. (C) showing well formed fibrous tissue (Hematoxylin and eosin, original magnification $\times 200$).

measured only at points without gross and histological evidence of necrosis or fibrosis were as follows: anterior $12 \text{ cm} \pm 0.1$, lateral $11 \text{ cm} \pm 0.1$, posterior $11 \text{ cm} \pm 0.2$, and septal $11 \text{ cm} \pm 0.1$. These wall thickness measurements were compared with those of patients who died from recurrent infarctions without a clinical diagnosis of ischemic cardiomyopathy (Table III) and with those of patients with primary valvular insufficiency and primary myocardial disease. The mean anterior, posterior, lateral, and septal wall thickness, as well as the total average wall thickness for the group with ischemic cardiomyopathy, was significantly thinner than the wall thickness of patients with recurrent infarctions, valvular insufficiency, or primary myocardial disease ($p < 0.01$, unpaired t test).

Examination of the coronary tree in the 14 patients with ischemic cardiomyopathy revealed multiple vessel involvement by atherosclerosis in all patients. In seven patients, three major vessels were narrowed 75% and in seven patients, two vessel involvement was present (average 2.5 major coronary arteries). None of the patients

had significant left main disease and all of the patients had well developed collaterals visible by postmortem angiogram (Fig 2). Of the 14 patients, seven (50%) had infarcted or scarred papillary muscles and seven (50%) had mural thrombi. By gross and histological evaluation, one patient had only one remote myocardial infarction, but one which involved 50% of the left ventricular circumference. Seven had two infarcts, four had three infarcts, and two had four infarcts, all involving at least two vascular distributions. Of the 14 patients, 12 had anterior infarctions (four transmural, eight subendocardial), nine had posterior infarctions (one transmural, eight subendocardial), and eight had lateral infarctions (three transmural, five subendocardial).

The amount of infarcted myocardium determined by planimetry ranged from 8% to 46% (average 25%). In only four patients (28%) was more than 30% of the left ventricle involved, and in four patients less than 20% of the myocardium was infarcted. Histologic examination showed well formed myocardial scars in all hearts. In the

Table I Clinical findings

| Number of patients | 14 |
|---------------------------------|--------------------------------|
| Age | 40-81 (avg 62 yrs) |
| Sex | 3 females (21%) 11 males (80%) |
| Diabetes | 3 (21%) |
| Hypercholesterolemia | 3 (21%) |
| Myocardial infarction | 8 (64%) |
| Angina pectoris | 6 (42%) |
| Congestive heart failure | 14 (100%) |
| Electrocardiogram | |
| Remote myocardial infarction | 5 (36%) |
| Acute myocardial infarction | 2 (14%) |
| Conduction disturbances | 7 (50%) |
| Atrial arrhythmias | 3 (21%) |
| Ventricular arrhythmias | 7 (50%) |
| Chest radiograph | |
| Cardiomegaly | 14 (100%) |
| Increased pulmonary vascularity | 3 (21%) |
| Pulmonary edema | 6 (42%) |

To compare ventricular wall thickness and over all topography 12 patients who died from recurrent myocardial infarctions 16 patients with chronic primary valvular insufficiency (eight mitral regurgitation eight aortic regurgitation) and 16 patients with primary congestive cardiomyopathy were selected from the autopsy files

Results

Of over 200 cases studied 14 were identified which fulfilled the clinical criteria for ischemic cardiomyopathy

Clinical findings The clinical data of the 14 patients are summarized in Table I. The patients ranged in age from 40 to 81 years (average 62 years) with 11 of 14 being male. None of the patients had a history of hypertension or alcohol abuse. Of the 14 patients three had diabetes mellitus (21%) and three had hypercholesterolemia (21%). Nine patients (64%) sustained a remote myocardial infarction by history six patients (42%) had angina pectoris and all 14 had longstanding symptoms of severe intractable congestive heart failure. In none of the 14 patients were the electrocardiograms normal but in only half of the patients were the changes diagnostic for myocardial infarction. The electrocardiogram revealed remote myocardial infarction in five patients (36%) and acute infarction in two (14%). Conduction disturbances were frequent in these patients three (21%) had a left bundle branch block two (14%) a right bundle branch block and two had a left anterior

Table II Causes of death

| | No of patients and % |
|--|----------------------|
| Ventricular tachycardia/ventricular fibrillation | 7 (50%) |
| Hypotension | 2 (14%) |
| Acute myocardial infarction | 1 (7%) |
| Intractable heart failure | 4 (29%) |

hemiblock. Three of the patients were in atrial fibrillation and three had recurrent episodes of ventricular tachycardia. Cardiomegaly on chest radiograph was noted in all patients and nine patients (64%) had radiographic evidence of congestive heart failure at their most recent examination.

The immediate causes of death of the patients are shown in Table II. Seven patients (50%) died suddenly of documented ventricular arrhythmias two (14%) from hypotension one from an acute myocardial infarction and four (28%) from intractable heart failure.

Autopsy findings The average heart weight was 625 grams with a range of 450 to 830 grams. All the hearts had biventricular dilatation with no evidence of discrete aneurysm formation (Figs 1 and 2). Although the average total heart weight (625 grams) and the average left ventricular weight (290 grams) were above normal and indicative of cardiac enlargement the maximal left ventricular wall thickness was not increased. The average maximal left ventricular wall thickness

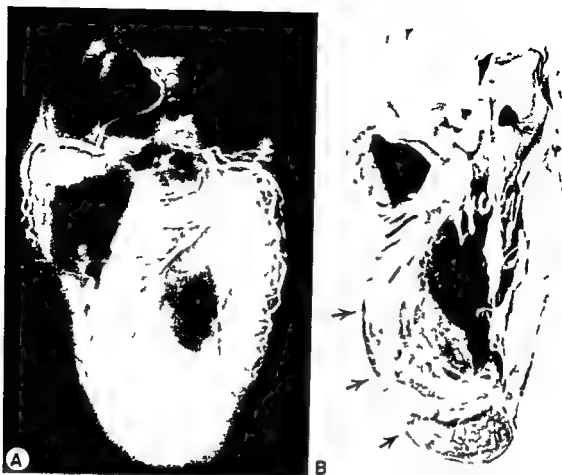


Fig 3 Shown here are a postmortem angiogram (A) and a gross specimen (B) of a heart with an anteroapical aneurysm of the left ventricle. Although the infarct is large and the coronary disease severe in contrast to ischemic myocardiopathy the heart here shows marked regional wall dilatation rather than a diffuse myocardiopathic type of dilatation. Thrombus is layered within the aneurysm (arrows).

tion.* We have been able to identify only three reports describing autopsy findings in ischemic cardiomyopathy^{3,6,12} and in only three patients were the studies detailed. What distinguished the heart in ischemic cardiomyopathy from the heart of patients with prior infarctions and no evidence of left ventricular dysfunction remained unclear. In this study of 14 autopsied patients with ischemic cardiomyopathy we examined several possible determinants of the diffuse left ventricular dysfunction including severity and extent of coronary disease, total amount of left ventricle injured by old and new infarction, heart size and wall thickness.

As observed by others from clinical studies,¹ a prominent feature of these patients was the severity of their coronary disease. All had critical narrowings in at least two major coronary arteries and multiple lesions within at least one of these major vessels. Half of the patients

had > 75% narrowing in all three major vessels. Severe coronary disease alone is not sufficient, however, to cause ischemic cardiomyopathy. Most patients with coronary artery disease with and without infarction do not have congestive heart failure.

All the hearts studied here with ischemic cardiomyopathy had grossly evident myocardial infarction. Although one might surmise that the size of the infarction is a major determinant of ischemic cardiomyopathy as it has shown to be for cardiogenic shock,¹³ findings here suggest that the multiple sites of injury rather than the extent of the injury may be more important. Our patients showed as little as 8% and as much as 46% of the left ventricle involved by infarction with an average of 25% infarction for the group. Of the 14 patients four had less than 20% of the myocardium lost by old or new infarction. In 13 of the 14 patients, however, infarcts were multiple.

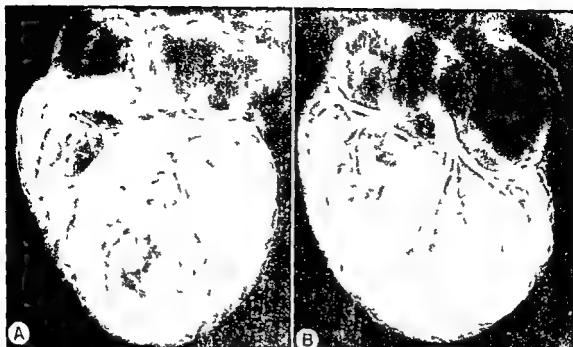


Fig 2 Postmortem angiogram from another patient with ischemic cardiomyopathy (A) again showing a globular diffusely dilated heart that has a similar shape to the heart in primary dilated cardiomyopathy, an example of which is shown in B. The coronary arteries in A are severely diseased but in B they are normal.

there was evidence of recent infarction as well but in each the recent infarcts were small involving less than 10% of the left ventricular wall. The non infarcted myocardium histologically revealed focal myocardial cell hypertrophy, foci of interstitial and perivascular fibrosis but no other evident or characteristic abnormality.

Discussion

In 1969 Rafferty and associates¹ reported four patients with a congestive cardiomyopathy who at catheterization had severe three vessel coronary artery disease. They concluded that chronic ischemic heart disease could present as a cardiomyopathy and that before a diagnosis of primary congestive cardiomyopathy is made, occlusive coronary disease must be excluded. In 1970 Burch and colleagues² coined the term 'ischemic cardiomyopathy' for those patients with coronary artery disease and severe ventricular dysfunction. Two autopsied patients were studied who had focal fibrosis, ventricular hypertrophy and ventricular dilatation. Dash and co-workers³ presented their findings of 30 patients who had congestive heart failure and at cardiac catheterization had coronary artery disease, decreased left ventricular ejection fraction (< 0.48) and wide

spread left ventricular wall motion abnormalities.

In this study 14 autopsied patients with ischemic cardiomyopathy were studied. Clinically all patients had heart failure with cardiomegaly and none had a history of hypertension or chronic alcoholism. Although all patients had pathologic evidence of severe coronary artery disease and infarction, only 64% had a history of myocardial infarction and only 42% had angina pectoris. Two patients (14%) did not have a history of angina pectoris or myocardial infarction. Furthermore, in three patients the presence of bundle branch block on the electrocardiogram and the lack of a clear cut history of myocardial infarction led to a clinical diagnosis of primary myocardial disease. One of the most striking electrocardiographic abnormalities in these patients was the frequency of ventricular dysrhythmias. Eight patients had a history of recurrent ventricular ectopic beats and three had prior documented ventricular tachycardia or ventricular fibrillation.

These clinical features of ischemic cardiomyopathy are compatible with the reports of others.¹⁻⁴ What has received little attention however are the pathologic features of the heart in this condi-

hypertrophy is a reflection of the intrinsic idiopathic myocardiopathic process in ischemic cardiomyopathy it seems likely that the severity of coronary disease and the limitations in blood supply combined with multifocal myocardial scarring limit the ability of the wall to respond appropriately to the demands of increased wall tension secondary to cavity dilatation

Summary

Ischemic cardiomyopathy has been defined clinically as congestive heart failure occurring in patients with coronary artery disease without coexisting hypertension primary valvular disease ventricular aneurysm formation or known causes of cardiomyopathy Morphologic definition of this entity is scarce We reviewed over 200 patients with coronary artery disease who came to autopsy at this hospital and identified 14 who met the above criteria At autopsy all the hearts showed diffuse biventricular dilatation without aneurysm formation All had evidence of recurrent infarction in more than one vascular distribution and postmortem angiography revealed extensive coronary artery disease The amount of infarcted myocardium determined by planimetry ranged from 8% to 46% Although the hearts were enlarged with an average weight of 600 grams the non infarcted ventricular myocardium was thinner than seen in normals in patients with ischemic heart disease without cardiomyopathy in patients with idiopathic congestive cardiomyopathy and in those with dilatation due to valvular regurgitation The results suggest that ischemic cardiomyopathy does not merely reflect a critical amount of myocardium lost but rather severe diffuse coronary artery disease accompanied by multiple sites of infarction which together lead to progressive dilatation disproportionate wall thinning and inadequate compensatory wall thickening Thus these patients appear to have a

true cardiomyopathy in that the entire left ventricle (infarcted and non infarcted tissue) appears to be adversely affected by the ischemic process insofar as there is a diffuse globular remodeling of the heart

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Table III Ventricular wall thickness of non infarcted myocardium

| | Group I — Ischemic cardio- myopathy | Group II— Recurrent infarctions | Group III— Primary valvular insufficiency (aortic or mitral insufficiency) | Group IV— Idiopathic dilated cardiomyopathy |
|------------------------------------|---|---------------------------------------|--|---|
| anterior wall thickness (mean) | 1.20 cm (± 0.10) | 1.7 cm (± 0.10) | 1.9 cm (± 0.10) | 1.7 cm (± 0.10) |
| posterior wall thickness (mean) | 1.10 cm (± 0.20) | 1.7 cm (± 0.11) | 1.9 cm (± 0.10) | 1.6 cm (± 0.10) |
| lateral wall thickness (mean) | 1.10 cm (± 0.10) | 1.7 cm (± 0.11) | 2.0 cm (± 0.10) | 1.7 cm (± 0.10) |
| septal wall thickness (mean) | 1.10 cm (± 0.10) | 1.6 cm (± 0.07) | 1.9 cm (± 0.10) | 1.6 cm (± 0.10) |

Group I measurements were significantly less than those in the other three groups ($p < 0.01$)

nd were in the distribution of more than one major coronary artery. It appears that when the nature loss of myocardium is in one vascular distribution the area of regional injury shows maximal dysfunction and the non infarcted myocardium undergoes compensatory wall thickening. If cardiac dilatation occurs it is apt to be regional or aneurysmal. If the injury occurs in multiple vessel distribution in the setting of extensive coronary disease diffuse rather than regional dilatation is apt to occur. That such dysfunction and diffuse dilatation can occur with as little as 20% loss of left ventricle might suggest that diffuse ischemia combined with multisite injury might contribute to the progressive cardiac dilatation of ischemic cardiomyopathy.

What is perhaps one of the most striking feature of the heart in ischemic cardiomyopathy is that it takes on the over all globular configuration of a dilated congestive cardiomyopathic heart (Fig 2) a configuration to be readily distinguished from the heart with discrete left ventricular aneurysm which might have as severe dysfunction and as great a total extent of infarction (Fig 3). Although the clinical presentation of these two entities left ventricular aneurysm and ischemic cardiomyopathy may be indistinguishable their morphologic characteristics and likely their potential for surgical remedy are markedly different. With improved noninvasive techniques which provide information on overall shape such as the two dimensional echocardiogram and the thallium 201 myocardial perfusion scan the two entities should be identifiable.

All 14 hearts were markedly enlarged with an average weight of 625 grams but left ventricular

wall thicknesses were disproportionately thin for heart weight even in areas not directly thinned by necrosis or fibrosis. The average maximal wall thickness in these hearts was significantly thinner than the values obtained from a group of autopsied patients with recurrent infarctions but without a myocardial picture ($p < 0.01$) and the walls were thinner than the values obtained for autopsied patients with idiopathic dilated cardiomyopathy ($p < 0.001$) and with primary valvular disease ($p < 0.01$).

Congestive heart failure and myocardial infarction are a recognized stimulus for myocardial hypertrophy in patients with coronary artery disease. The ability of surviving myocardium to hypertrophy in response to injury of part of the left ventricle is a compensatory mechanism however only to a point in that it leads to additional tissue requiring additional coronary flow. Rackley and co workers have shown that the degree of left ventricular hypertrophy relative to left ventricular end diastolic volume was a prognostic indication of post catheterization survival rates with greater hypertrophy for a given end diastolic cavity enlargement carrying a better outlook. It has also been shown in patients with primary myocardial disease that the ability of the heart to compensate for its dilatation by developing wall hypertrophy correlated positively with survival. The patients with ischemic cardiomyopathy studied at autopsy appear to fall into that poorer prognostic group in which the heart is dilated but it not able to appropriately thicken adjacent non infarcted wall. Although in primary cardiomyopathy one might suspect that the inability of some patients to develop compe-

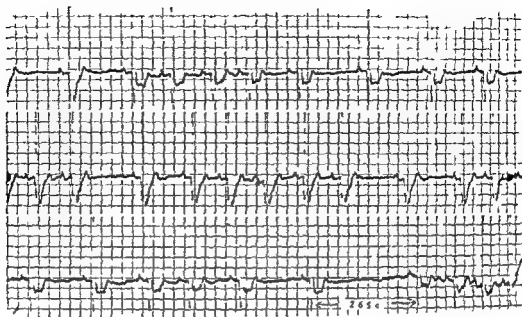


Fig 1 The electrocardiogram indicates frequent sinus pauses (the longest being 2.6 seconds)

at the nose or mouth with a CO₂ analyzer. Thoracic breathing movements were determined by measuring transpulmonary pressure changes with an intraesophageal balloon. Upper airway obstruction was defined as a cessation of airflow at the nose and mouth in the presence of continued thoracic breathing movements. All investigational procedures were carried out with the subject's informed consent under protocols approved by the local Human Experimentation Committee. The pre-tracheostomy study revealed 312 upper airway obstructions with a mean duration of 16 seconds with a range of 10 to 27 seconds. Obstructions were accompanied by prolonged asystole (up to seven seconds) with second degree AV block and marked sinus arrhythmias (Fig 2). O₂ saturations during sleep ranged from 82% to 93%. The post-tracheostomy study revealed no upper airway obstructive episodes and no clinically significant central apneas or other respiratory abnormalities. There were no significant cardiac arrhythmias. The ear oximeter revealed no oxygen desaturations during the study.

Electrophysiologic studies. From a right femoral vein puncture a tripolar catheter was positioned on the septal leaflet of the tricuspid valve and resting A-H and H-V intervals were recorded. The A-H interval representing AV nodal conduction was 140 msec and the H-V interval representing His-Purkinje conduction was normal at 50 msec. This catheter was switched for a hexapolar catheter which was positioned in the high right atrium in order to study the response of the sinus node to overdrive pacing. The patient had a maximum sinus recovery time of 910 msec and a correct sinus recovery time of 260 msec, which indicated normal sinus node function. She had normal atrioventricular conduction during rapid atrial pacing.

Discussion

There is little information on arrhythmias in the sleep apnea syndrome. Kryger and associates⁴

reported a case of an obese man who had somnolence and upper airway obstruction. His apneic episodes were usually associated with bradycardia, rhythmias. He had atrial fibrillation and flutter with a high degree AV block and asystole lasting up to ten seconds. The arrhythmias were abolished by atropine but electrophysiologic studies were not performed. Tilkian and colleagues⁵ studied cardiac arrhythmias during wakefulness and sleep in 15 patients with sleep induced obstructive apnea. Sleep was characterized by marked sinus arrhythmia in 14, by extreme sinus bradycardia in six, by asystole or 2.5 to 6.3 seconds in five, by complex PVCs in ten, and by ventricular tachycardia in two. Atropine was partially effective and tracheostomy highly effective in preventing the majority of these arrhythmias during sleep. Tilkian and co-workers⁵ also postulated that these arrhythmias are not due to fixed or anatomic disease of the sinoatrial or AV nodes but that they reflect functional and reversible abnormalities precipitated by sleep-related abnormal CNS functioning. They suggested that airway obstruction caused hypoxia which stimulated vigorous inspiratory effort against the closed airway. This inspiratory effort activated vagal parasympathetic impulses causing severe bradycardia. Hypoxia and acidosis may also increase sympathetic tone, causing sinus tachycardia, PVCs, and ventricular tachycardia.

Table 1 illustrates the data in our patient.

Case reports

Arrhythmias in sleep apnea

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The original description of the Pickwickian syndrome included obesity, periodic breathing with hypoventilation, somnolence, and cor pulmonale.¹ It is now well established that the essential features of this syndrome—i.e., somnolence, hypoventilation, and cor pulmonale—can occur in the absence of obesity and with normal carbon dioxide responsiveness.² This syndrome has been recently called the sleep apnea hypersomnolence syndrome (SAHS) because of the occurrence of obstructive apnea in these patients during sleep.³ Disturbances in cardiac rhythm can occur during sleep,^{4,5} and multiple arrhythmias have been described in association with the SAHS. In this report I describe detailed sleep studies, electrophysiologic studies, and the clinical data of a patient with the SAHS and briefly present arrhythmias of other patients with this syndrome.

Case report

History A 33-year-old black female was admitted to the University Hospital on December 9, 1976, because of "sleep trouble." She complained of falling easily to sleep even when she was teaching at a kindergarten. Her mother noticed that she fell asleep very easily when she was working. She had frequent morning headaches. Her mother also confirmed that the patient snored noisily and had frequent periods of apnea. A hospital record indicated that she had been obese for many years prior to that time. She had adenocarcinoma of the endometrium with polycystic ovarian disease and underwent a total vaginal hysterectomy with bilateral salpingo-oophorectomies in 1974. Physical examination on admission revealed a very obese black female who appeared older than her stated age and weighed 174 kg. The blood pressure was 130/90 mm Hg, pulse was 97 per minute, and respiratory rate was 22 per minute. The skin was dry. The head, eyes, ears, nose, and

throat were unremarkable. There was thyromegaly, but no palpable nodes. The carotid pulses were 2+ bilaterally. The chest was symmetrical with equal bilateral expansion. The breasts were huge and pendulous without palpable masses. The lungs were clear to auscultation and percussion. The heart was regular in rhythm without murmurs or gallops. The abdomen was massive with fat pads. The extremities were obese without edema. Neurological examination was within normal limits. She had a normal CBC with differentiation SMA16. T3 and T4 arterial blood gases revealed pH 7.47, P_{CO} 37 mm Hg, P_O 72 mm Hg, and HCO₃⁻ 27 mEq/L. Electrocardiograms were all within normal limits with sinus rhythm. A chest x-ray was free of active infiltrates and the heart size was normal. Pulmonary function studies revealed a reduced total lung capacity, functional residual capacity, residual volume, and expiratory residual volume, all compatible with mild restrictive disease. The diffusing capacity and airway resistance were within normal limits.

A sleep study was performed. She experienced over 300 episodes of upper airway obstruction with some lasting over 30 seconds. These were accompanied by severe cardiac arrhythmias. The details will be described subsequently. Tracheostomy was performed because of disabling somnolence and severe cardiac arrhythmias. She was discharged without medications. She had lost some weight and did well with marked reduction in daytime somnolence and headache. Hypersomnolence was quickly resolved and the post-tracheostomy sleep study revealed no cardiac arrhythmias.

Approximately one week prior to her second admission on April 15, 1977, she developed constant throbbing headaches with blurred vision. She came to the emergency room where her pulse was noted to be slow. An electrocardiogram showed frequent sinus pauses (Fig. 1). She was admitted to the Intensive Care Unit. Physical examination showed that she was somewhat confused. Blood pressure was 112/70 mm Hg and her pulse was irregular. She weighed 163 kg at this time. Other physical findings were unchanged from those of the previous admission. Arterial blood gases revealed pH 7.49, P_{CO} 8 mm Hg, P_O 11 mm Hg, and HCO₃⁻ 20.5 mEq/L. The ECG monitor showed frequent episodes of sinus bradycardia, sinus pauses, and second-degree heart block not associated with respiration or hypoxia. One milligram of atropine was given without effect.

Sleep studies. In order to determine the presence and extent of upper airway obstruction during sleep, the patient was studied in the Sleep Physiology Laboratory. Recordings included continuous monitoring of the ECG, EEG, EOG, and EMG for determination of sleep stages. The presence of airflow was assessed by recording fluctuations of expired CO₂.

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Table I

| Name | Age | Sex | Med | ECG | Arrhythmia during sleep studies | Trach | Arrhythmia after trach | Ref's |
|------|-----|-----|-----------|---------------|---------------------------------|-------|------------------------|--------|
| JR | 47 | M | Amuno Dig | Mild RVH | 7 sec SP SB 30 Slow VT | (+) | (-) | 17 kg |
| BB | 30 | M | None | NL | 36 sec SP | (-) | | 13 kg |
| H.C | 24 | F | None | 1st A V block | 70 sec. ASY 2 A V block | (+) | (+) | 153 kg |
| OC | 58 | M | None | IRBBB | 16 sec SP | (-) | | 131 kg |
| CU | 30 | M | None | Mild RVH | 65 sec SP | (+) | (-) | 99 kg |
| CT | 64 | M | None | NL | Freq PVC's VT | (-) | | 140 kg |
| FW | 48 | M | None | NL | Junct Rhy | (-) | | 125 kg |

Abbreviations: Amuno = amorphyllin Dig = digitalis NL = normal RVH = right ventricular hypertrophy IRBBB = incomplete right bundle branch block SP = sinus pause SB = sinus bradycardia VT = ventricular tachycardia Junct Rhy = junctional rhythm Trach = tracheostomy
Freq = frequent

See text for details

not have clinical evidence of organic heart disease, sinoatrial or AV nodal disease is not likely. I can hypothesize that increased parasympathetic impulses because of vigorous inspiratory effort against the closed airway caused sinus bradycardia, prolonged sinus pause, and AV block. After abrupt cessation of the airway obstruction, the parasympathetic tone decreased and there would have been overshoots of sympathetic impulses which could have caused frequent premature ventricular contractions and ventricular tachycardia.

Conclusion

Severe cardiac arrhythmias can be seen in patients with sleep apnea. These are not likely to be caused by the organic sinoatrial or AV node disease but are due to functional and reversible abnormalities precipitated by the sleep-dependent CNS dysfunction. Tracheostomy may be effective in controlling the arrhythmias in some patients with obstructive sleep apnea.

Summary

A 23-year-old black female was referred to the University Hospital of Oklahoma because of sleep trouble. She complained of falling asleep easily during the daytime. A sleep study was performed which showed prolonged apnea up to 35 seconds and prolonged asystole up to seven seconds with second degree heart block. A tra-

cheostomy was performed. She had lost some weight and did well until six months later when she developed severe throbbing headache and visual blurring. She came to the emergency room and an ECG showed sinus bradycardia and prolonged sinus pauses up to 26 seconds, first and second degree AV block. She had hypoxia and atropine was ineffective. Electrophysiologic studies were performed. Details of the case are described and mechanisms of the arrhythmias are discussed.

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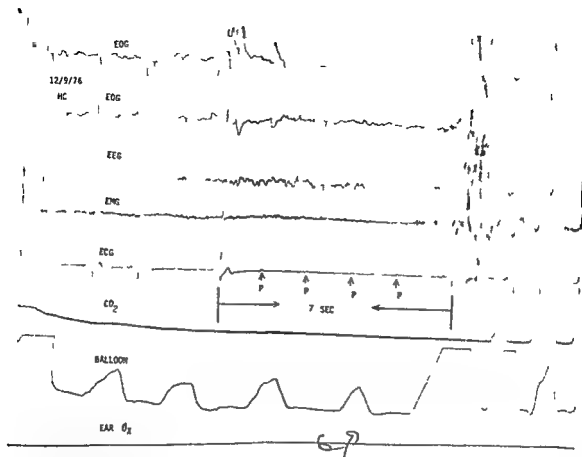


Fig 2 Polygraphic sleep study The flat line of CO indicated prolonged apnea in the presence of breathing efforts shown by fluctuations in the line of the balloon There were 7 seconds of asystole associated with apnea As soon as the patient started breathing normal sinus rhythm was restored EOG = electrooculogram EEG = electroencephalogram EMG = electromyogram CO = CO analyzer BALLOON = intraesophageal balloon P = P wave

They are all obese (except patient C U) and young (except patient C T) and none had a history suggesting ischemic heart disease and none were on cardiac medication except patient T R Waking ECGs were not impressive During sleep they all had significant cardiac arrhythmias Sinus arrhythmia (not listed here) occurred in all patients in association with episodes of upper airway obstruction Patients C V and T R had no arrhythmias after a tracheostomy

Only patient H C (the subject of this case report) had electrophysiologic studies She had prolonged asystole (seven seconds) with second degree AV block before tracheostomy Arrhythmias persisted after tracheostomy however they were much milder We gave atropine intravenously which was not effective and arrhythmias were not associated with hypoxemia This suggests another mechanism of arrhythmia in the patient

Since electrophysiologic studies were normal during wakefulness sinoatrial or AV nodal disease is not likely Then what are the mechanisms of arrhythmia in the patient? As shown in Fig 2 she had airway obstruction with inspiratory effort evidenced by the flat CO line and the cyclic shift of the line of balloon During this airway obstruction the parasympathetic nerve must have been activated which could have caused second degree heart block with prolonged asystole It is interesting to note that she was well for six months after a tracheostomy and when she developed arrhythmias she had severe headache and she was somewhat confused Thus we can hypothesize that an acute central nervous event may have caused these arrhythmias although she had no other evidence of CNS dysfunction

How about the mechanism of the other patients? Since most of them are young and did

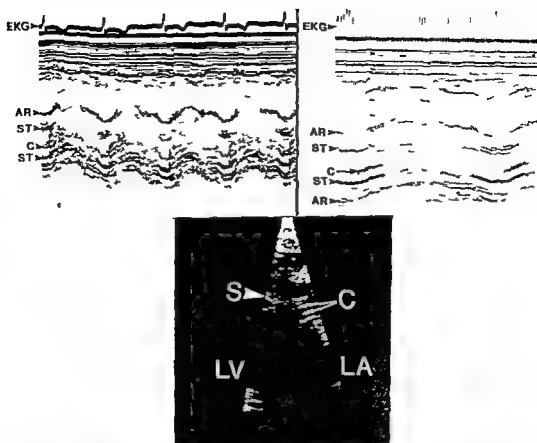


Fig 1 M mode and two dimensional echocardiogram of the stenotic porcine aortic valve are shown. Left upper panel increased cusp echoes with restricted cusp motion during systole are depicted. Right upper panel after reducing the coarse gain the high frequency low amplitude fluttering of the thickened cusps (C) are visualized. Lower panel a systolic frame of the two dimensional echocardiogram is shown. Note the marked reduction (<10 mm.) of the cusp opening. AR = aortic root C = cusps EKG = electrocardiogram LA = left atrium LV = left ventricle S = ventricular septum ST = porcine valve stents

phy but was clearly reduced on the two dimensional study. This is comparable to the previous reports in which the two dimensional echocardiography because of its greater spatial orientation was found to be more useful than the M mode study in assessing the valve opening and stenosis of the native aortic valve. The systolic opening of the porcine cusp however as with the native aortic valve may be influenced by left ventricular stroke volume. The left ventricular function and stroke volume were normal in our patient and would not account for the reduced cusp opening of the porcine valve.

The significance of the systolic fluttering noted on the M mode study of our patient cannot be determined. Similar flutter has been reported in a normal native aortic valve but has not been observed in a normally functioning porcine aortic valve.³ It is possible that the systolic flutter may be a normal finding which has not yet been reported in the relatively small number of echo-

cardiographic reports dealing with the function of a normal porcine bioprosthesis in the aortic position. Another possible explanation of systolic flutter may be as a result of turbulent blood flow across the stenotic and thickened porcine cusps. Further studies are needed in this area before firm conclusions can be drawn.

The etiology of porcine valve stenosis is not exactly clear. Most likely it is a result of a degenerative process similar to that previously reported by light and electron microscopic studies of these valves.⁴

In conclusion both modes of echocardiography are of value in evaluating stenosis of the porcine aortic valve. A condition which may be amenable to valve replacement surgery.

Summary

M mode and two-dimensional echocardiographic features are reported in a patient who developed severe stenosis of a porcine xenopro-

Echocardiographic features of a stenotic porcine aortic valve

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The echocardiographic features of porcine valve degeneration have recently been reported. These reports have confined their descriptions to aortic insufficiency, mitral stenosis and insufficiency occurring in the degenerating porcine xenograph. Although stenosis of the porcine valve in the aortic position has been noted to occur, the echocardiographic features were not described due to the inability to visualize the valve adequately. Subsequent to our initial reports we have observed an additional patient with stenotic degeneration of the porcine xenograph in the aortic position that occurred 60 months after implantation.

Case history

D D, a 3-year-old male underwent an aortic valve replacement with a porcine xenograph (Hancock) valve six years later he was seen again complaining of pressure like chest pain and dyspnea on minimal exertion. He also complained of frequent light headed spells, without syncope. There was no history of paroxysmal nocturnal dyspnea, fever or chills.

Physical examination revealed a blood pressure of 120/80 mm Hg, pulse 80/minute and regular. The carotid pulse upstroke was prolonged and a systolic thrill was palpable in the second right intercostal space. The aortic component of the second heart sound was diminished. A grade IV/VI systolic ejection murmur radiating to the carotid vessels and Grade II/VI diastolic blowing murmur were present at the second right intercostal space and the lower left sternal border. The diastolic murmur had not been present on a physical examination performed a year previously and the intensity of the systolic murmur had increased.

Pertinent laboratory studies including hemoglobin, platelet

total and differential white blood count and blood cultures were all within normal limits. The electrocardiogram revealed left ventricular hypertrophy with strain pattern. Chest x ray revealed left ventricular enlargement and on fluoroscopy porcine valve calcification was noted. Cardiac catheterization revealed a peak porcine aortic valve gradient of 88 mm Hg with calculated valve area of 0.3 square centimeters. Angiography revealed moderate porcine aortic valve insufficiency with normal coronary arteries.

An M mode and a two-dimensional echocardiogram using conventional techniques and instrumentation (Smith Kline Ekoline 20-A and Ekosector 1) were performed within one week of cardiac catheterization and porcine valve replacement surgery. Both modes of echocardiography revealed an increase in porcine cusp echoes (Fig. 1). The M mode study in addition revealed high frequency, low amplitude systolic fluttering of the cusps. The opening of the valve could not be accurately measured on the M mode study due to increased echoes from the thickened cusps. The systolic opening of the porcine cusps however was clearly visualized and was markedly reduced on the two-dimensional study (Fig. 1).

The gross examination of the porcine valve at the time of surgery revealed thickened and stenotic cusps with multiple calcific nodules and scarred retraction of the cusp margins (Fig. 2).

Discussion

M mode echocardiography has been reported to be useful in evaluating a stenotic mitral porcine valve.¹ Although severe stenosis of a porcine valve has also been reported in the aortic position,² the echocardiographic features of this entity have not been reported. The increased cusp echoes in our patient were associated with thickening and calcification of the valve cusps which was demonstrated at the time of surgery. Echocardiographic features of the stenotic porcine valve in the mitral position have shown a similar increase in cusp echoes with identical gross anatomic findings.¹ As a result of increased cusp echoes, the porcine valve opening could not be clearly demonstrated by M mode echocardiogra-

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Intraventricular thrombosis in polycythemia vera A cause of intractable cardiac failure

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Case report

A 72 year-old man was hospitalized for massive edema of the legs, increase in abdominal girth of recent onset weakness and anorexia. He had previously been healthy and he specifically denied antecedent hypertension or heart disease. A diagnosis of congestive heart failure was made on the basis of findings of cardiomegaly pitting dependent edema ascites hepatomegaly and bilateral basal pulmonary rales.

Pertinent laboratory data were as follows: hemoglobin 18.4 Gm/dl, hematocrit 63% RBC 6.73 million/cu mm WBC 13,100/cu mm with 48% mature neutrophils 8% bands 18% lymphocytes 2% eosinophils and 1% basophils platelets 30,000/cu mm. Leukocyte alkaline phosphatase score was 162 (control 76). Total blood volume was 19,500 ml (predicted value 5,000 ml), the red cell mass was 9,000 ml (predicted value 2,500 ml). The results of serum chemical analysis were as follows: LDH 790 MU/ml (laboratory normal 90 to 200 MU/ml) SGOT 90 MU/ml (laboratory normal 0 to 50 MU/ml) total bilirubin 3.8 mg/dl total protein 5.8 Gm/dl albumin 2.94 Gm/dl urea acid 9.5 mg/dl BUN 19 mg/dl calcium 8.1 mg/dl and alkaline phosphatase 90 MU/ml (laboratory normal 30 to 80 MU/ml). The serum electrolyte values were within normal limits except for a slightly elevated value for serum sodium of 148 mEq/L. Chest

roentgenogram demonstrated an enlarged heart, pleural effusion. Gastrointestinal series and intravenous urogram studies were normal except for displacement of the right and left kidney by an enlarged spleen. Liver scan with ¹⁹⁹Au showed hepatomegaly without focal lesions. The ECG showed ST-T wave abnormalities. Bone marrow aspiration was dry but a biopsy showed promyeloid hyperplasia megakaryocytosis, eosinophilia, fibrosis.

With the clinical diagnosis of congestive heart failure secondary to arteriosclerotic coronary artery disease patient was treated with digitalis diuretics and phlebotomy. Lowering of hematocrit to below 50% was achieved by phlebotomies. However the congestive failure proved intractable and he died 6 months later of refractory congestive failure with left pleural effusion massive ascites, and anasarca.

Pathology

At autopsy the heart was hypertrophied and weighed 300 grams, the maximum thickness of the right and left ventricular wall being 0.3 and 1.8 cm respectively. A large intramural thrombus covering the endocardial surface of the left ventricle in its entirety was observed. The thrombus extended from the apex of the heart and reduced the capacity of the left ventricle by about 75% (Fig. 1). Microscopically the thrombus displayed various stages of organization. The portion exposed to the blood flow was well endothelialized. The major branches of both the right and left coronary arteries showed minimal arteriosclerotic changes. No significant narrowing of the arterial lumina was demonstrable. The myocardium beneath the intramural thrombus was studied by multiple sections. No evidence of any recent or remote infarction was observed.

In the gross examination of the various viscera, anasarca passive venous congestion was observed especially in the lungs and the liver. The liver weighed 2,400 grams, and on section showed a nutmeg appearance. The large pulmonary arteries showed prominent arteriosclerotic plaques. The spleen was massively enlarged weighed 1,200 grams and on serial sections displayed many areas of infarction. Histologically pronounced extramedullary hematopoiesis and

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Fig 2 This figure shows the gross appearance of the stenotic porcine valve. The cusps are thickened with multiple calcific nodules and retracted cusp margins.

valve implanted in the aortic position. The presence of increased cusp echoes along with reduced cusp opening was the most consistent echocardiographic finding in this patient. The clinical and the echocardiographic findings were subsequently confirmed by cardiac catheterization and surgery.

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Summary

The occurrence of thrombotic events is central to the course of polycythemia vera.¹ Myocardial cerebral peripheral and pulmonary infarctions are frequent and are consequences of thromboses in small and medium caliber arteries. Thrombosis in large caliber arteries is a rare event. Thrombosis within the chambers of the heart has not been hitherto reported.

This report documents the occurrence of massive left ventricular thrombosis in a patient with polycythemia vera. The thrombus reduced the left ventricular capacity by about 75% and caused intractable congestive heart failure.

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Fig 1 Massive intraventricular thrombus. The thrombus surface is smooth and well-endothelialized (AA); the underlying myocardium shows no evidence of recent or old infarction (BB).

sinusoidal proliferation was observed in the spleen; the splenic infarcts showed various stages of organization. Extramedullary hematopoiesis was also observed in the liver, the lungs, and the retroperitoneal and mediastinal lymph nodes. In the lungs, muscular hyperplasia of peripheral, subpleural arteries was observed. The marrow displayed pronounced hyperplasia involving all the marrow elements: megakaryocytes and eosinophils were especially abundant.

Discussion

Cardiac function and cardiac output are usually normal in polycythemia vera.⁶ The clinical course of the patient reported in this paper was highly unusual while the diagnosis of polycythemia vera was readily made by the hematologic studies and blood volume determinations; the true nature of its relationship with congestive heart failure remained masked. The probability of the cardiac failure being secondary to arteriosclerotic coronary artery disease or the existing hematologic disorder was clinically suspected though the electrocardiographic evidence for this was lacking. At autopsy, the clinical picture of refractory heart failure was related to the presence of the left ventricular thrombus; per se, reference to the literature on intracardiac tumors and thrombi shows that tumors in the right heart are associated with weakness, edema, hepatomegaly, and ascites. Space-occupying lesions in the left heart are associated with dyspnea, orthopnea, and with emboli to the central nervous system, renal, mesenteric, and peripheral arteries. In view of the closer correspondence of this patient's clinical manifestations to those of

patients with compromised right ventricular function, we offer the hypothesis that this patient's thrombus either interfered with mitral valve function or so gradually but progressively interfered with left ventricular filling that the process became a physiological equivalent of mitral stenosis with the subsequent development of pulmonary hypertension and right ventricular failure. From a functional standpoint, the pathogenetic mechanism for the intractable heart failure seen in this patient is closely analogous to the hemodynamic impairment observed in patients with endomyocardial fibrosis.⁷ In this entity, found primarily among Africans, the fibrotic process with or without thrombus formation may so seriously reduce the ventricular capacity as to prove fatal.

Rheologic factors are known to play an important role in the local propagation of clotting. It is likely that this clot formed slowly by accretion on a small starting nidus. The large size of the clot, the many stages of organization seen in the thrombus, the completely endothelialized surface, the absence of an acute arterial occlusive event, and the prolonged (6 month) course of this patient are all consistent with this hypothesis. The nature of the event initiating the intraventricular clotting was obscured by the reparative processes within the clot.

Had echocardiographic studies been performed, the clot might have been detected.⁸ Its removal might have restored the left ventricular capacity and relieved intractable congestive failure.

Summary

The occurrence of thrombotic events is central to the course of polycythemia vera.¹ Myocardial cerebral peripheral and pulmonary infarctions are frequent and are consequences of thromboses in small and medium caliber arteries. Thrombosis in large caliber arteries is a rare event. Thrombosis within the chambers of the heart has not been hitherto reported.

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Echocardiographic diagnosis of left ventricular thrombi

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Although left ventricular thrombi are frequently found at postmortem examination¹ and can be identified angiographically² in many patients with cardiovascular disease they have only recently been identified by echocardiographic techniques.³ Reports of their recognition are still few and the M mode and cross sectional echocardiographic appearances of the clots have been variable. Presented below are two patients with left ventricular thrombi recognized echocardiographically and documented by pathologic and/or angiographic examination whose M mode and cross sectional echocardiograms add to the spectrum of echocardiographically detectable ventricular clot. The sensitivity and specificity of echocardiographic techniques in the diagnosis of intracardiac thrombi are discussed.

Methods

The M mode and cross sectional echocardiographic studies in each patient were performed with the patient's chest elevated 15 degrees and with the patient turned 30 degrees into a left lateral position.

M mode echocardiograms were obtained using

an Irex 101 or System II Ultrasonoscope coupled with a 2.25 MHz transducer focused at 7.5 cm. They were recorded on an Irex System II recorder. The echocardiographic transducer was placed along the left sternal border in the third or fourth intercostal space and was angled inferiorly and laterally to record echoes from the left ventricle. An attempt was made to scan toward the apex.

Cross sectional echocardiographic scans were obtained in multiple planes using the 80 degree Varian Model 3000 Phased Array Sector Scanner. A long axis view of the heart approximating a sagittal plane was obtained by positioning the transducer in the third or fourth intercostal space to the left of the sternum and directing the plane of the sweep from the inferior wall of the left ventricle to the base of the heart. An attempt was made in each patient to visualize the apex in the sagittal plane by placing the transducer at the position of the apical impulse and directing the plane of the sweep superiorly and inferiorly. Such a change in transducer position is necessary for visualization of the left ventricular apex in the sagittal plane since in most patients an echocardiographic scan from the apex to the base of the heart involves changing the plane of the echocardiographic sweep. Short axis (transverse) views of the left ventricle were obtained by positioning the transducer along the left sternal border or at the apex (for a transverse view of the apex) and directing the plane of the sweep perpendicularly to the long axis of the heart along an imaginary line connecting the left shoulder and the right hip. Four chambered views from the apex were

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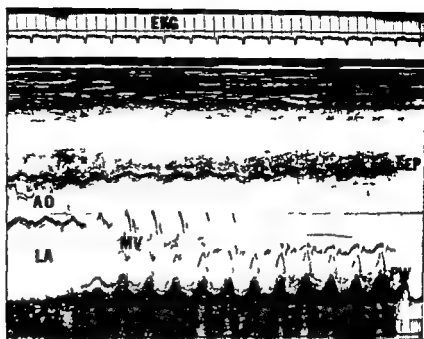


Fig 3 M mode echocardiographic scan from the aortic root (AO) and left atrium (LA) to the left ventricle in Patient No 1 after removal of 78 grams of left ventricular thrombus. The left ventricle remains enlarged. The septum (SEP) is dyskinetic. MV = mitral valve. PW = posterior left ventricular wall. EKG = electrocardiogram.

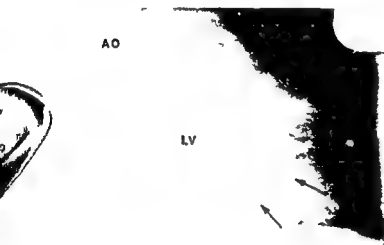


Fig 4 Left ventriculogram in the right anterior oblique projection in Patient No 2. Angiographic dye fails to fill the entire left ventricle due to the presence of a large apical mural thrombus which appears to be adherent to the left ventricular wall. Arrows demonstrate the border between dye and mural thrombus. AO = aortic root. LV = left ventricular cavity.

wall moved well and because the thrombus appeared to be confined to the apex on cineangiographic study. It is perhaps more likely that the band of echoes represented an echo producing pericardial effusion with adhesions between epicardium and pericardium resulting in movement of the pericardium. If so failure to identify

thrombus by M mode echocardiographic technique may have been due to the inability to scan down into the apical region. On cross sectional echocardiographic examination a well-defined echocardiographic density was observed adjacent to and moving with the ventricular apex. A pericardial effusion was apparent. Angiographic findings were diagnostic of a left ventricular thrombus which appeared firmly adherent to the apical wall.

Although left atrial and left ventricular thrombi are found far more frequently at postmortem examination than are primary or secondary intracardiac tumors,^{1,2,3} reports of their recognition by echocardiographic techniques have been relatively few⁴⁻¹³ compared to multiple reports of echo diagnosis of intracardiac neoplasms.¹⁴⁻¹⁶ In a study by Ports and associates⁴ of 61 patients with surgically proven left ventricular thrombi none were detected by M mode echocardiography and only the four largest thrombi were detected by cross sectional techniques. In another study by DeMana and co-workers⁵ cross sectional echocardiography detected densities compatible with apical thrombus in five patients who experienced peripheral emboli following myocardial infarction. The M mode echocardiograms in those patients revealed no signs of thrombi. The ability of echocardiographic tech-

areas of firm white tissue thought to represent focal organization. The right and left brachial artery emboli were identified as recent thrombus.

Postoperative M mode echocardiography (Fig 3) revealed disappearance of the previously noted intraventricular echoes. The patient made a satisfactory recovery and was discharged on the sixteenth postoperative day on digoxin and sodium warfarin. Ventricular ectopy was markedly diminished on no medications. Following discharge however progressive severe congestive heart failure developed and the patient died seven months after surgery.

Case report No 2

P D a 32 year old man with a history of anterolateral transmural myocardial infarction four months previously was admitted to Beth Israel Hospital for cardiac catheterization to evaluate post myocardial infarction angina pectoris. Medications included propranolol and nitrates.

On physical examination the pulse was 80 and regular the blood pressure was 130/80 mm Hg and the weight was 238 pounds. There was no evidence of jugular venous distension, rales, murmurs or gallops. The electrocardiogram revealed changes of an old anterolateral myocardial infarction. The chest x ray was normal, without cardiomegaly or evidence of failure. Cardiac catheterization revealed an elevated left ventricular filling pressure of 17 mm Hg, a cardiac index of 2.6 liters per minute and an ejection fraction of 44%. The left ventricle was dilated and there was paradoxical motion of the anterior wall and apex. A large apical left ventricular filling defect was present and appeared to be adherent to the left ventricular myocardium (Fig 4). The right coronary artery was occluded proximal to the crux. The left coronary artery had diffuse irregularities but no apparent critical stenosis. Surgery was not recommended.

M mode and cross sectional echocardiography were performed following cardiac catheterization. The M mode echocardiogram (Fig 5) revealed a markedly dilated left ventricle measuring 8.2 cm in diameter. The septum which measured 11 mm in thickness in end-diastole moved paradoxically and failed to thicken with systole. The posterior wall demonstrated normal systolic motion but there were multiple echoes from the posterior wall of the heart measuring 22 mm in end-diastole. The cross sectional long axis and four-chambered apical views (Fig 6) demonstrated an intraventricular mass adherent to the left ventricular apex. The mass was well defined and both it and the underlying myocardium moved dyskinetically. There was no apparent pericardial effusion on the cross-sectional views.

Discussion

The echocardiographic appearances of intracardiac thrombi are variable.¹¹⁻¹³ Left atrial thrombi have been recognized by abnormal linear densities or by masses of echoes within the left atrium.^{6-11,13} The appearances of left ventricular thrombi have ranged from fine dust like densities¹ to more discrete clusters or bands of echoes adherent to the septum or occupying the apical region of the left ventricular cavity.⁴ The echocardiographic findings in our two patients add to

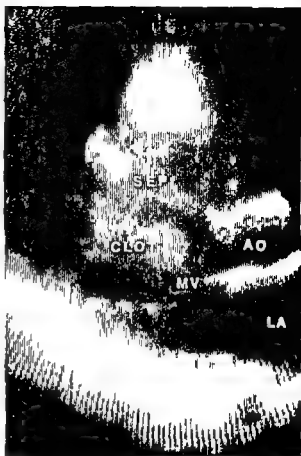


Fig 2 Preoperative cross sectional recording of the heart in Patient No 1. A dense mass of echoes representing the surgically confirmed clot, is seen to fill much of the left ventricular cavity during diastole. The mass appeared freely mobile and without obvious attachment to the septum (SEP) or mitral valve leaflets (MV). During systole the echogenic mass was seen to move further into the left ventricular outflow tract. AO = aortic root. LA = left atrium.

the reported spectrum of appearance of intracardiac thrombi. In the first patient a dense mobile mass of echoes was seen to partially fill the left ventricular cavity and appeared during systole to move into the left ventricular outflow tract. There was no apparent connection of this mass to the left ventricular wall on either M mode or cross sectional echocardiographic examination. The movement pattern of the mass seen well on the cross sectional study would make differentiation from a mobile intraventricular neoplasm such as a ventricular myxoma impossible. In the second patient it is unlikely that the M mode echocardiographic appearance of abnormal thickness of the posterior wall represented thrombus adjacent to myocardium because the posterior

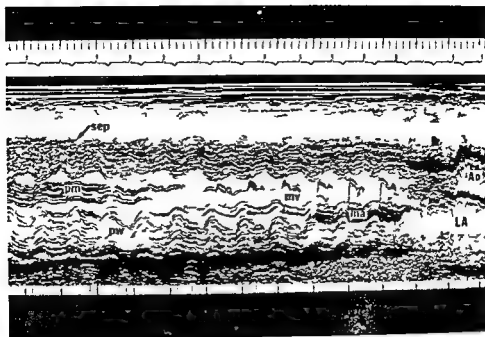


Fig 7 Slow scan from the apex of the left ventricle to the aortic root (AO) and left atrium (LA) in a hypertensive patient with severe concentric hypertrophy of the septum (SEP) and posterior wall (PW). A thick dense band of echoes representing a hypertrophied papillary muscle (PM) is seen within the left ventricular cavity. MV = mitral valve; MA = mitral annulus.

metastatic neoplasms may produce echocardiographic patterns similar to thrombus. Normal intracardiac structures which have become thickened or calcified may cause abnormal echoes within the left ventricular cavity. Due to failure of lateral resolution, a calcified mitral valve annulus may, on M mode or cross sectional echocardiographic study, appear to extend inferiorly into the left ventricular cavity.² Calcified chordae or papillary muscles¹ may give the appearance of a dense intraventricular mass. In such cases, cross sectional echocardiography may help to clarify the origin of abnormal echoes seen on M mode study because it allows better recognition of anatomic relationships and movement of structures relative to one another. This is illustrated by the recent study in our laboratory of a 32 year old woman with a long history of hypertension and left ventricular hypertrophy. Severe concentric left ventricular hypertrophy was noted on the echocardiographic studies with septum and posterior wall both measuring 23 mm. The mitral annulus appeared calcified. With scanning inferolaterally toward the left ventricular apex on M mode echocardiography (Fig 7), a dense mass of echoes, similar to that seen in patient No 1, was observed to partially fill the left ventricular cavity. On one dimensional exam-

ination, those echoes appeared to be separate from septum and posterior wall. However, the two dimensional echocardiogram revealed that the abnormal mass of echoes represented papillary muscle continuous inferiorly with the apical ventricular wall and superiorly with chordae giving support to the mitral valve leaflets (Fig 8).

The cases presented serve to further illustrate the variable echocardiographic appearances of left ventricular thrombi and emphasize the potential difficulties of differentiating them from other intracardiac structures or masses. Strict attention to echocardiographic technique may improve the sensitivity of echocardiography in the detection of left ventricular thrombus. Since thrombus is located most commonly in the left ventricular apex,² an attempt must be made to scan inferiorly and laterally toward the apical region on M mode examination. A slow sweep from the apex to the base of the heart may allow recognition of focal wall thickening which may be produced by overlying mural thrombus. The use of multiple cross sectional views, such as the long and short axis views with the transducer placed at the apex and the four chambered apical view,¹ should allow optimal study of the apex and improve the sensitivity of cross sectional echocardiography in the detection of thrombi.

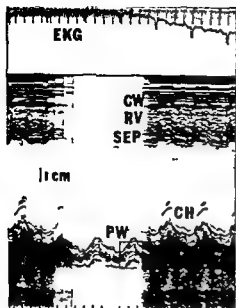


Fig 5 M mode echocardiographic recording from Patient No 2 shows a dilated left ventricle. The septum (SEP) move paradoxically and fails to thicken during systole compatible with prior infarction. Multiple echoes (PW) measuring 22 mm in width at the end of diastole are recorded from the region of the posterior wall and pericardium. EKG = electrocardiogram CW = chest wall RV = right ventricle CH = chordae 1 cm = one centimeter

niques to identify thrombi is probably limited by several factors. First the thrombus may be too small to be recognized. Secondly the echocardiogram will be unable to record echoes from a thrombus if the sound beam is not directed toward the mass. Since many left atrial thrombi are located within the atrial appendage, a part of the heart not visualized by routine echocardiographic scanning, recognition of those intra atrial thrombi by usual echocardiographic techniques is not possible. Most left ventricular thrombi are located in the apex of the left ventricle² and will not be visualized unless the beam can be directed toward the apex. The apparent increased sensitivity of cross sectional echocardiography over M mode echocardiography in the recognition of left ventricular masses³ is probably in part due to the ability of cross sectional techniques to visualize many more regions of the heart, particularly if multiple echocardiographic planes are examined. Finally, the difference in acoustic impedance of blood and thrombus or of ventricular wall and thrombus may be insufficient for adequate reflection of sound waves at their interfaces. Ports and colleagues³ noted that those thrombi recognized



Fig 6 Cross sectional echocardiographic recording of the four-chambered apical view in Patient No 3 shows a large echogenic mass adherent to the ventricular wall and filling the apex (clot). LV = left ventricle LA = left atrium RV = right ventricle RA = right atrium. The electrocardiogram is below the echo.

echocardiographically had layers of organized thrombus alternating with areas of more recent thrombus formation. In the first patient presented above the thrombus seen readily by echo techniques as a dense mass of echoes also contained areas of fresh thrombus as well as areas of organized thrombus. If such inhomogeneity is associated with differences in acoustic impedance such layered thrombi may produce sufficient reflection of ultrasound to allow their recognition. This is likely since it is known that the reflection characteristics of body tissues are in large part dependent on their content of collagenous fibers.

Unfortunately, echocardiographic patterns suggestive of thrombus may not be specific. Variations in gain and reject settings and reverberations may produce spurious echoes within an intracardiac chamber. Intracardiac primary and

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Since the echocardiographic patterns are not specific for thrombus however other possibilities must be considered when an abnormal mass of echoes is demonstrated. Those would include artifacts, primary or metastatic tumors and normal intracardiac structures which have become more intensely echo producing due to alterations in their size, anatomic position within the heart or acoustic impedance properties.

Summary

Left ventricular thrombi have not been commonly recognized by M mode or by cross section echocardiographic techniques despite their frequency at postmortem examination in patients dying of cardiovascular disease. We discuss two patients with left ventricular thrombi recognized echocardiographically and confirmed by pathologic and/or angiographic evaluation whose M mode and cross sectional echocardiographic abnormalities add to the variable spectrum of appearance of left ventricular thrombi. The sensitivity and specificity of echocardiographic techniques in the diagnosis of intracardiac thrombi are discussed.

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Fig 8 Cross-sectional long axis, diastolic view of the heart in the patient with left ventricular hypertrophy demonstrates the severe thickening of the septum (VS), posterior wall (PW) and papillary muscle (PM). The tip of the arrow points to chordal attachments between the anterior leaflet of the mitral valve and the papillary muscle. A calcified mitral annulus is seen below the base of the arrow. AO = aortic root, LA = left atrium. The electrocardiogram is below the echo.

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Table I Classification of interventions used to reduce indices of infarct size in patients or infarct size in animals

| | <i>Reduction of experimental infarct size</i> | <i>Effect on indices of infarct size in patients</i> |
|--|--|--|
| 1 Relief of vascular obstruction | | |
| Antithrombotic agents | Heparin reduces tissue necrosis | Reduces ST segment elevation ¹⁴ |
| Antiplatelet agents | Aspirin does not alter thrombus | Not tested |
| Relief of spasm Ca antagonists | Complex action including increased collateral flow specific reduction of contractility in ischemic zone ² and afterload reduction | Reduction of load on heart and of ST-elevation and reduction of predicted enzymatic infarct size in 9 of 11 patients |
| 2 Increased collateral flow or diffusion to ischemic zone | | |
| Nitrates | Increased collateral blood flow ¹⁵ | See Tables V VIII and references 190-193 |
| Hyaluronidase | Reduces QRS changes and necrosis | See Tables V VII and reference ¹⁹⁶ |
| Intra aortic counterpulsation | Reduces ischemic injury | Not tested but see reference 236 |
| Surgical reperfusion | Data controversial see reference 2 | Not tested |
| 3 Relief of load on heart | | |
| Nitrates (see also Section 2 Table I) | Reduces load ¹⁶ ST \uparrow ¹⁷ CK preservation ¹⁸ | ST \downarrow with intravenous NG ¹⁹ for sublingual NG see references 191-197 |
| Nitroprusside | Controversial effects | Controversial effects on ST segment, see references 200 and 244 |
| Other vasodilators | | |
| Ca antagonists | Reduction of necrosis | Reduction of predicted infarct size |
| Diazoxide | No data | Increased ECG changes in 9 of 10 patients |
| Ganglion blockade | For general effects of afterload reduction see reference 1 | Trimethaphan reduces predicted infarct size |
| 4 Catecholamine antagonists | | |
| β blocking agents | ST \downarrow CK preservation lessened necrosis | ST \downarrow less CK release improved metabolism see Table II |
| α blocking agents (phentolamine) | Not documented | Only hemodynamic data ²⁴ |
| 5 Specific metabolic measures | | |
| Increased provision of oxygen | Reduction of infarct size ²⁵ | ST elevation \downarrow |
| Inhibition of fatty acid metabolism | Decreased enzyme release | ST elevation \downarrow |
| Glucose insulin potassium | Decreased necrosis improved metabolism ²⁶ | Inotropic effect without CK effects ²⁴ |
| Calcium antagonists (see Relief of spasm) | | (see above) |
| Prevention of severe cellular acidosis | Not fully tested may be effective | Not tested |
| Stabilization of membranes | Steroids reduce ischemic injury ²⁴ and infarct size ²⁷ with mummification ²⁸ | Controversial effects reduce Q wave for mation |
| Prevention of cell swelling | Mannitol reduces necrosis only after temporary ischemia ²⁹ but not after prolonged occlusion | Not tested |

series of fundamental papers in 1963 showed that pronethalol which lacked intrinsic sympathetic activity could relieve angina pectoris in patients with ischemic heart disease. Pronethalol was soon superseded by propranolol which strangely had no apparent effect on angina in its first trial¹³ although propranolol is now established as a major advance in the therapy of angina. Many of the more recent studies are with the cardiospecific agent practolol which has a certain amount of intrinsic sympathetic activity but now cannot be used for long term therapy because of serious

undesirable side effects. Of the large number of β blocking agents currently available relatively few have been tested in patients with acute myocardial infarction (Table II). The more recent recognition that similar factors to those precipitating angina can act to increase ischemic damage in developing infarction (see Fig. 1 Part 1) made it logical to search for effects of β blockade on infarct size.

In view of the established effects of propranolol on heart rate and afterload reduction and the recently reported effects on collateral flow (see

Reviews

Myocardial infarct size Part 2 Comparison of anti infarct effects of beta blockade glucose insulin-potassium nitrates and hyaluronidase

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Based on the principles discussed in the first part of this review the following interventions (Table I) could be expected to limit infarct size (1) relief of vascular obstruction (2) increased collateral flow or diffusion to the ischemic zone (3) relief of the load on the heart thereby promoting a more favorable balance between the oxygen supply and demand (4) catecholamine antagonism and (5) specific metabolic measures Table I lists those agents tested in patients for therapeutic effects on indices of infarct size Because the role and exact nature of the vascular obstruction is so controversial agents acting at that level have been omitted from further consideration and one agent has been selected from each of the remaining categories (2 to 5) of Table I

Thus the four anti infarct agents selected for consideration in further detail are β blockade glucose insulin potassium nitrates and hyaluronidase β blockade is selected because of the exceptionally full experimental and clinical studies now available and because of a combined hemodynamic and metabolic action Glucose insulin potassium is selected as one of the first interventions introduced and now well studied over many years it is an agent likely to counteract undesirable metabolic changes in acute infarction Glucose insulin potassium is compared with the use of a nicotinic acid analog which also has an antilipolytic action Nitrates

are selected because of their dual mechanism of action both by causing coronary vasodilation and by reducing the pre and afterload on the heart In addition nitrates as therapeutic agents are well known to all practicing cardiologists Nitroprusside is considered together with the nitrates although nitroprusside has a more definitive effect on the afterload than do nitrates Finally hyaluronidase is chosen as a well investigated agent with minimal side effects and no known hemodynamic mode of action

Other promising agents have been omitted although of great potential interest because of the limited number of patient studies available For example the effects of steroids are well documented in experimental preparations Although they diminish the features of acute ischemic injury probably acting by means of membrane stabilization they also inhibit wound healing and hence increase the risk of ventricular rupture or aneurysm (See also Table I references 250 251 256 and 257) Another interesting category of agents the calcium antagonists are only now being studied in patients

1 β blockade

Effects of propranolol on ischemia Black in 1957 searched for a compound to improve ischemia by reducing the effects of sympathetic stimulation and decreasing the myocardial oxygen demand¹ The dichloro analog of isoproterenol was the first compound found to inhibit the adrenergic receptors of the heart but the marked stimulant effect on the heart rate (intrinsic sympathetic activity) obviously limited the therapeutic potential of this type of compound.² A

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Table III Contraindications to β blockade used in various studies

| Parameter | Definition | Author |
|----------------------|---|---|
| 1 Heart failure | Clinical Cardiomegaly Severe dyspnea Crepitations 3rd heart sound venous pressure exceed ing 3 cm above sternal angle Signs of poor peripheral circulation—eg., coldness or pallor Cardiac index < 2.5 Radiological Interstitial edema or pulmonary edema but pulmonary venous congestion accepted | Mueller et al Waagstein and Hjalmarson Barber et al. ^a Waagstein and Hjalmarson Gold et al. Peter et al. ^a |
| 2 Hypotension | Systolic cuff pressure 110 mm. Hg < 100 mm. Hg Mean arterial pressure < 75 mm. Hg | Mueller et al. ^a Waagstein and Hjalmarson ^a |
| 3 Bradycardia | Rate below 80/min Rate below 60/min Rate below 60/min Rate below 45/min. | Gold et al. Gold et al. Mueller et al. Peter et al. Waagstein and Hjalmarson |
| 4 Conduction defects | No AV block AV block exceeding first-degree QRS duration not more than 100 msec. | Mueller et al. ^a Peter et al. Waagstein and Hjalmarson ^a |
| 5 Lung disease | History of chronic lung disease or asthma for propranolol | Mueller et al. ^a |
| 6 Age | Over 65 excluded for propranolol | Peter et al. |

The β blocking agents used are (a) Propranolol, ^a (b) Practolol or metoprolol ^a (c) Practolol ^a.

changes and the metabolic effects of β blockade are of much interest. Opie and Thomas² found that propranolol pretreatment reduced considerably the uptake of free fatty acid by the ischemic zone of coronary ligated dog hearts while the uptake of glucose was correspondingly increased. Their findings are in agreement with the increased respiratory quotient of the heart in patients given propranolol.¹⁰ The net metabolic effect was a change from the metabolism of free fatty acids to that of glucose with a decreased oxygen uptake.¹⁰

It is not possible at present to clearly decide whether it is the metabolic or the hemodynamic effects of β blockade which are of greatest importance. In patients^{1,2} substantial decreases in precordial ST segment elevation could be obtained by practolol even in those patients in whom the heart rate did not fall. But if the metabolic effects on fatty acids were of importance then drugs such as propranolol, oxprenolol and acebutolol which are antihypolytic should be considerably more effective than drugs such as metoprolol which are not antihypolytic.¹⁴ Proof of such distinctions is still awaited.

In summary, most experimental evidence shows that β blockade causes myocardial me-

chanical metabolic and blood flow effects which are favorable to the outcome of developing myocardial infarction.

Propranolol in patients with acute myocardial infarction. In patients with acute myocardial infarction (Table II) Gold and associates¹¹ recently reported that intravenous propranolol given to 12 selected patients caused an abrupt decrease in the ST segment elevation and decreased the incidence of arrhythmias. There were also substantial reductions in the arterial pressure, the heart rate and the cardiac output, but perhaps surprisingly heart failure did not develop as indicated by the pulmonary capillary wedge pressure which remained unchanged. In another important study, Mueller and co-workers¹ showed that although the myocardial oxygen consumption per beat was decreased by intravenous propranolol and the myocardial blood flow was slightly reduced nevertheless lactate metabolism improved.

These effects of propranolol on ischemia, as in patients have not yet been matched by studies with measurements of infarct size apart from the study of Peter and colleagues³ on highly selected patients. That study found decreased release of creatine kinase which was, however evident only

Table II β blocking agents used in patients with the clinical syndrome of acute myocardial infarction recent studies

| Authors | Agent | Route and dose | When given | Result |
|--|-------------|--|---|---|
| Mueller et al. ¹⁰ | Propranolol | 0.1 mg/kg in 3 divided doses at 5 minute intervals | 6-8 hours after admission for acute transmural myocardial infarction (including inferior infarction) | Improved myocardial metabolism slight rise (2 mm Hg) in pulmonary wedge pressure |
| Gold et al. | Propranolol | IV 0.15 mg/kg | Anterior myocardial infarction within 8 hours of onset with persistent pain | Cardiac output fell but pulmonary wedge pressure did not rise ventricular irritability decreased decreased ST-elevation |
| Peter et al. | Propranolol | IV 0.1 mg/kg over 10 min followed by 320 mg over next 27 hours | Within 12 hours of onset of typical ischemic chest pain with ECG evidence of ST-elevation or pathological Q waves | Decreased blood levels of creatine kinase if propranolol given within 4 hours of onset of symptoms |
| Fehdes et al. | Practolol | IV 0.0 mg | Up to 72 hours after onset of symptoms | Decrease of area and severity of ST elevation |
| Barber et al. | Practolol | Orally 300 mg b.i.d. | As soon as patient seen and then for 7 years | If initial heart rate exceeded 100 per min., mortality reduced at 3 months |
| Waagstein and Hjalmarson ¹¹ | Practolol | IV 5-30 mg (mean = 18 mg) | In coronary care unit as soon as possible after arrival | 1. Dramatic pain relief 2. Double product fell from 10,500 to 8,500 3. ST segment fell by 29% |
| Waagstein and Hjalmarson ¹² | Metoprolol | IV 15 mg | In coronary care unit as soon as possible after arrival | Similar effects to practolol but lower heart rate |
| Muholland and Pantridge | Sotalol | IV 10 mg plus atropine 0.6 mg IV | Before transport by ambulance | Prevention of tachycardia (110-120 per min.) during movement by ambulance better than practolol |
| Devlin et al. | Sotalol | IV 10 mg | Before transport by ambulance | Normal pre movement heart rate kept low |
| Helkila and Nieminen ¹³ | Pindolol | IV 0.2 mg | Within 15 hrs. of onset | Improves systolic wall motion by echocardiography |

Double product = systolic BP \times heart rate IV = intravenous.

below) it is not surprising that the majority of animal experimental work shows that propranolol can substantially reduce the extent of ischemic injury and of myocardial necrosis^{2, 3} (see also Opie and Thomas²) although there is no ready explanation for one discordant study⁴ in which propranolol in a high dose (5 mg/kg) had no effect. That study is especially difficult to understand because the same group found that propranolol reduced enzyme release in patients with infarction (see Table II). Other studies⁵ show that propranolol decreases the extent of enzyme depletion and the development of epicardial Q waves in the infarcting dog heart. However, a possible disadvantage of propranolol is the decreased coronary perfusion pressure which might explain why propranolol decreased the coronary flow in the ischemic zone of open-chest anesthetized dogs^{6, 7, 8}. The most recent infor-

mation from closed chest conscious dogs³ indicates that propranolol causes a favorable redistribution of the blood supply to the ischemic area. Important hemodynamic differences from open chest preparations are the greater decrease of heart rate in open chest dogs (higher pre propranolol rate) and the lesser cardiac dilatation following propranolol in closed chest dogs¹⁰.

In patients flow to the ischemic zone cannot directly be measured but indirect evidence suggests that propranolol improves the coronary flow relative to the metabolic demand¹⁰. Thus propranolol can be expected to have a beneficial effect on the infarcting myocardium unless there is heart failure when the heart can be expected to enlarge further as a result of decreased contractility.

Metabolic effects of β blockade Tissue necrosis ultimately depends on cellular metabolic

practolol given to patients with an initial heart rate exceeding 100 per minute improved the short term prognosis (Table II). A high heart rate during movement by ambulance can be prevented by sotalol (10 mg intravenously alone or with atropine 0.6 mg)^{133, 134} but an effect on ischemic injury was not proven. A randomized study in other situations—e.g. patients without heart failure in Killip groups 1 and 2—with positive effects on mortality would be required before β blockade could be recommended in other situations.

β blockade Summary The use of β blockade to limit ischemic damage in acute myocardial infarction has extensive experimental and clinical support. One report suggests that infarct size is limited in patients as shown by decreased rates of release of creatine kinase. Certain contraindications require strict observation to avoid undesirable side effects. Close monitoring of the patient is required. Both mechanical and metabolic factors may account for the improvements observed. There are insufficient data to recommend the general use of β blockade in patients with acute infarction.

2 Metabolic interventions—Glucose insulin potassium (GIK)

GIK as a polarizing agent Although GIK is now known to have a metabolic action very similar to that of propranolol (compare Opie and Thomas³ with Opie and Stubbs¹) GIK was first popularized by Sodi Pallares and his group¹ as a polarizing agent that could restore K⁺ loss from the ischemic zone and hence improve mitochondrial function. Their claim of improved K⁺ in the ischemic zone after experimental coronary occlusion has been questioned by Surawicz¹ but there is no real reason to doubt that K⁺ uptake can occur^{1, 2} and that tissue K⁺ can improve. Sodi Pallares' work led to the expectation that GIK could reduce arrhythmias in patients with acute infarction but numerous contradictory studies were conducted before the recent description of the natural history of arrhythmias in acute myocardial infarction led to the knowledge that by far the majority of lethal ventricular arrhythmias (fibrillation) occur within the first 3 hours of the onset of symptoms¹—i.e. before GIK was instituted in those studies. The antiarrhythmic effects of GIK have now been shown by Lown's group^{1, 3} who found that GIK elevated the ventricular fibrillation threshold in dogs.

Metabolic effects of GIK More recently, studies have shown that GIK can inhibit myocardial necrosis¹ as effectively as other anti-ischemic agents such as hyaluronidase¹. In the baboon, GIK helps to minimize ischemic tissue metabolic changes such as depletion of high energy phosphate compounds and of glycogen¹⁴¹. Opie and Owen¹⁴² studied the metabolic effects of GIK and found that it was especially effective on the border zone of the developing infarct when given for 6 hours after coronary artery ligation. However, it was also striking that GIK increased glycogen in all infarct zones and according to some workers the ultimate degree of necrosis is very closely linked to the degree of cardiac glycogen retention.¹³⁴ Thus it may be that when given over a longer period than 6 hours GIK is able to protect all zones against developing infarction. It should be stressed that GIK did not cause an accumulation of lactate or protons in the ischemic tissue¹⁴¹ in spite of the theoretical hazard of this supposed side effect.¹⁴³

The cellular metabolic effects of GIK in developing infarction were as follows.¹⁴⁰ The extraction of glucose increased relative to that of free fatty acid; cardiac glycogen increased and there was a switch from the metabolism of free fatty acid to that of glucose with decreased ST segment elevation. Similar metabolic effects can be achieved by propranolol in dogs¹⁴³ and in man.¹

To measure the maximal possible degree of conservation of oxygen induced by glucose insulin potassium we examined GIK effects on an isolated perfused rat heart preparation (Table IV). After coronary artery ligation the extent of the ischemic zone was measured by a supraventricular dye and by the severity of enzyme release. Changing the perfusate from a low potassium (3.0 mM) fatty acid solution to the addition of glucose insulin potassium (K⁺ = 5.9 mM) greatly decreased the release of enzyme and the apparent size of the ischemic zone while the mechanical efficiency (measured as joules/ml oxygen utilization) was increased. Thus compared with pure fatty acid utilization at a low perfusate K⁺, GIK markedly spared oxygen by improving efficiency by 60%. Similarly, excess FFA caused a deterioration of efficiency in non-chromic isolated pig hearts.¹⁴³ Although these data are not necessarily applicable to the more complex metabolic situation in patients,¹⁴⁴ yet the principle of metabolic oxygen wastage and mechanical inefficiency is stressed.

when propranolol was given within 4 hours of the onset of symptoms and even then was of border line significance ($P < 0.05$ $2 P < 0.1$ —usually it is the two tailed value for P which is quoted)

β blocking agents other than propranolol (Table II) Patient studies with β blocking agents other than propranolol are also shown in Table II and again the beneficial effects are apparent but again data on infarct size are missing. The agent best researched in man, practolol, reduces pain, ST elevation and short term mortality in patients with an initial heart rate exceeding 100 per minute "when practolol is started at a dose of 300 mg every 12 hours within 3 hours (median value) of the onset of symptoms. Although practolol has undesirable side effects with long term usage, there would appear to be no reason why short term practolol should not be used to institute treatment to be followed by another β blocking agent. Another cardio-specific β blocker, metoprolol, also reduces pain and ST elevation when given intravenously in the early stages of myocardial infarction (see Table II).

The long term beneficial effect of β blockade in reducing sudden death after anterior myocardial infarction has been shown for practolol¹⁴ similar data exist for alprenolol¹⁵ which like practolol possesses intrinsic sympathetic activity. But in neither study could the long term effects be ascribed to reduction of infarct size because the β blockade was started after the acute phase was over. Theoretically it is incorrect to extrapolate from results obtained with practolol to results that might be expected with another β blocking agent such as propranolol which has no intrinsic sympathetic activity. It remains possible that the presence and amount of intrinsic sympathetic activity is important in secondary prevention and it could be argued that only agents with such activity should be used for situations in which practolol has proved effective. Other agents with intrinsic activity include oxprenolol, pindolol, alprenolol and acebutolol but the amount of intrinsic activity varies. Because of the different properties of different β blocking agents it has been argued that it is unethical to promote drugs other than the tested ones (practolol, alprenolol) for post infarct protection and the same arguments should hold for the acute phase.

Sowton and associates¹⁶ and Shanks¹⁷ have argued that it is the β blocking qualities which are of most importance and that additional qualities are of no real therapeutic significance.

Although many clinicians seem to feel that the use of agents with intrinsic sympathetic activity in acute myocardial infarction leads to fewer problems with bradycardia, documentation of this theoretically possible view is not yet available. Very recently a challenging research report suggests that dimethylpropranolol, an agent without β blocking activity, can protect against ischemic reperfusion damage.¹⁸

Contraindications to β blockade (Table III) Each of the above cited studies used certain definite contraindications as listed in Table III. It is of interest that the majority of workers did not require monitoring by invasive procedures such as Swan Ganz catheterization or measurements of the cardiac index to assess whether beta blockade should be instituted or discontinued.

β blockade: Claims and counterclaims In brief, β blockade given in the acute phase is claimed to counteract the manifestations of acute ischemia and to improve the short term prognosis in patients. Studies on the effects of infarct size in patients are not yet at hand, although the rate of release of creatine kinase may be diminished by propranolol (P values borderline by one method of analysis).¹

The major arguments against the use of β blockade therapy rest on the possible harmful side effects. Occasional patients may develop high grade heart block requiring a pacemaker and the dangers of hypotension or heart failure also exist. One of 95 patients treated by Peter and associates¹ required balloon counterpulsation for heart failure thought to be precipitated by propranolol. Although these side effects are rare, especially in closely monitored and carefully selected patients, they are all too visible in comparison with the invisible effects of reduction of infarct size. Whether such potential side effects of β blockade are real hazards, awaits further studies. The decision whether or not to use β blockade in a given patient must depend largely on the skill and discretion of the attending physician and his views on the desirability of reduction of ischemic injury and (possibly) infarct size and on the status of the patient (Table III). In view of the harmful effect of a high heart rate on ischemia (see Fig 4 Part I), it is theoretically desirable to reduce a tachycardia not caused by heart failure or infection, i.e. an inappropriate tachycardia. Support for this view stems from the observations of Barber and colleagues¹ that oral

electrical stimulation of the heart with acute coronary occlusion

However, recently Heng and colleagues¹⁶³ showed that when high blood glucose values of 400 to 600 mg/100 ml were maintained in patients with acute myocardial infarction infarct size failed to decrease which is not surprising because the high blood glucose must be acting as a positive inotropic agent.¹⁷⁷ Thus, when GIK is given extreme hyperglycemia should be avoided unless the inotropic effect is specifically desired. In patients Sodi Pallares¹⁷⁸ recommended blood glucose values of between 120 and 140 mg/100 ml but tolerated values between 70 and 160 mg/100 ml. However higher values of an average of 286 mg/100 ml were accepted by Rogers and co workers.¹⁶

GIK and infarct size The study of Heng and associates¹⁶³ is one of the only two studies that have measured infarct size. The numbers studied by Heng and colleagues¹⁶³ were too few to permit any firm conclusions as also conceded by the authors. Furthermore the time after the onset of symptoms and the infarct size were too variable to allow tight grouping of the patients. A larger randomized trial assessing the effects of GIK, is now underway¹⁸⁰ and may give clearer guidance on the possible value of GIK in acute myocardial infarction. Present indications are that GIK reduced circulating free fatty acids and both the incidence of ventricular premature systoles and ventricular tachycardia. Survival appeared to improve but enzymatically estimated infarct size did not change. However the major rise of free fatty acids occurs in the first 1 to 3 hours of the onset of symptoms,⁷⁹ thus only when GIK is given very early could 'oxygen sparing' be expected.

GIK Claims and counterclaims Although one nonrandomized trial¹⁶ strongly suggests that GIK may improve mortality rate in patients with infarction Heng and co workers¹⁶³ felt impelled to stop their much smaller trial. However they did not consider that excess hyperglycemia (see above) could be adversely affecting the development of the infarction by increasing heart work (mean arterial pressure and pulmonary artery end-diastolic pressure increased) in their study. In fact the data of Heng and associates¹⁶³ could be interpreted to show that GIK may be a useful agent when an inotropic agent is required which appears not to extend infarct size even this

conclusion cannot be reached with certainty on the basis of the small numbers studied by Heng and colleagues¹⁶³ but it is in keeping with carefully documented dog data¹⁷³ and with ventricular function studies in patients.¹⁸¹

Another situation for which GIK should be considered is the presence of severe heart failure with a low sodium syndrome.¹⁸

GIK was also reported as reducing the incidence of heart block in an uncontrolled study but the potassium in GIK can promote prolonged A-V conduction in normal subjects at normal potassium levels.¹⁸² Thus more cautions are required on patients with heart block.

GIK Summary GIK has attracted considerable attention as being one of the first anti-infarct agents studied. Experimental evidence shows that GIK reduces infarct size. GIK has some propranolol like effects on heart metabolism including oxygen conservation. The majority of clinical studies have not been conducted in the light of modern knowledge of the natural history of arrhythmias and the patterns of development of infarct size occurring after the onset of acute myocardial infarction nor has the effect of infarct size been assessed in most studies in man. The results of a randomized study now underway will give better guidance on the possible use of GIK in acute myocardial infarction. GIK may have a place as an inotropic agent not increasing infarct size.

3 Reduction of the load on the heart and increased collateral flow by nitrates

Nitrates coronary vasodilation vs load reduction Amyl nitrite was used at the end of the last century for relief of angina by Lauder Brunton,¹⁸³ who noted the association of increased arterial pressure with the anginal attack and found that amyl nitrite relieved the pain and decreased arterial pressure. Many years later Robinson¹⁸⁴ found that for a given patient the double product of heart rate and systolic pressure required for the production of angina was relatively constant. He concluded that the advantage of the hypotensive action of nitrate outweighed its action on producing tachycardia. Furthermore venodilation was held to be the cause of decreased ventricular end-diastolic pressure.¹⁸⁵ It is evident that apart from the tachycardia nitrates produce reduction of the preload and the afterload changes which should be conducive not only to

Electrocardiographic effects of GIK Two experiments published by Calva and colleagues¹ are of particular historical interest because they antedate the current interest in the epicardial electrocardiogram generated by the work of Maroko and Braunwald.¹⁰ In the GIK treated heart in spite of the ST-elevation initially being greater the final Q wave formation was less.

GIK dosage Although Sodi Pallares has had extensive experience of GIK in patients neither his work nor the MRC trial¹⁶ were conducted in conditions which are directly relevant to our modern knowledge of the development of acute myocardial infarction. Thus in the MRC trial the average time elapsed since the onset of symptoms and the start of the GIK infusion was 24 hours or more in nearly 90% of patients by which time infarct size may largely be fixed (although reinfarction can still occur) furthermore the doses used were low and the glucose was sometimes given orally and the insulin subcutaneously (see Table V). Rogers and associates¹⁷ have shown that the effects of intravenous GIK in the early phases of acute myocardial infarction require assessment. Rogers and co-workers¹⁸ have shown that GIK (given into the right atrium as 300 g glucose 80 mEq potassium and 50 units soluble insulin per liter at the rate of 1.5 ml/kg/hr) is very effective in bringing down circulating free fatty acids in patients. When GIK was given for 4 days it induced potassium gain and elevation of blood glucose. This investigating team noted a transient hyperkalemia in some instances¹⁸ and also found that the pulmonary wedge pressure did not rise with GIK treatment. It would nevertheless be important to search for GIK effects on pulmonary capillary wedge pressure in patients with left ventricular failure. The problem of hyperkalemia would be avoided by a variable potassium infusion as recommended by Sodi Pallares and Ponce de Leon.¹⁹

GIK as an antilipolytic intervention Thus reduction of plasma free fatty acids is an important effect of GIK (Table IV). Lipolysis can also be inhibited by a nicotinic acid analog. In pacing induced angina the degree of ST depression (but not the development of chest pain) was reduced as the circulating free fatty acids fell. Thus intervention also reduces acute ischemic injury in patients with infarction as judged by decreased precordial ST elevation and decreased arrhythmias.²⁰ However repetitive use of this agent throughout the first 24 hours of acute myocardial

Table IV GIK and efficiency of rat heart compared with effects of very high fatty acid low K perfusate (Opie and Bricknell unpublished data)

| | Efficiency (joules per ml O ₂) | Enzyme release (mU/g/hr) |
|--|--|--------------------------------|
| Hearts perfused with pathologically high fat ty acid and low K K = 3.0 mM | 3.10 ± 0.09 (40) | 330.8 ± 3.39* (14) |
| Hearts perfused with glu cose and insulin K = 9 mM | 4.93 ± 0.09 (50) | 6.699 ± 3.29* (1) |
| Change | +60% | -80% |

Effects of changing from 1 v h, high fat perfusate to GIK (as glucose 11 mM insulin 11 mU/ml K = 5.9 mM) in isolated perfused working rat heart with coronary ligation. Efficiency was measured by comparing the oxygen uptake with the work performance. Enzyme release was taken as an index of myocardial damage and was measured as release of lactate dehydrogenase from the coronary venous effluent. The mechanism of the altered efficiency induced by these extreme alterations of substrate (high fatty acid to GIK) is unknown but may include oxygen wasting. Note that as efficiency rises with GIK, enzyme release is greatly decreased. Mean values ± SEM.

infarction cannot be recommended because the blood free fatty acid values rebound unless high doses are used which cause significant side effects. In contrast GIK can consistently depress circulating free fatty acid values in patients with infarction without side effects or rebound.²¹ In addition however both GIK¹⁷ and addition of glucose²² can achieve their effects in the presence of unchanged circulating free fatty acid levels showing that GIK acts not only as an antilipolytic agent but also by promotion of glucose metabolism in animal models.

Danger of hyperglycemia Maroko and co-workers²³ found that hypertonic glucose by itself was nearly as effective as GIK in preventing necrosis after coronary occlusion in dogs. It is however important to note that the blood glucose concentration should not be allowed to rise to values which are too high. Sonnenblick and colleagues²⁴ injected hypertonic glucose into dogs shortly after coronary artery ligation the blood sugar rose to values of nearly 700 mg/100 ml while the contractility of the heart increased and the elevated end-diastolic pressure fell. The therapy reduced the incidence of ventricular premature beats and of ventricular fibrillation. The beneficial effect of hypertonic glucose on arrhythmias has been confirmed²⁵ in that intravenous glucose prevents the onset of ectopic beats after

Table V Mechanism of action of four anti infarct agents based on experimental data and/or clinical observations

| | Heart rate | BP | Contractility | Afterload | Metabolism | Microvascular damage | End \dot{V}_O_2 |
|---------------------------------|---------------------|---------|---------------|-----------|------------|----------------------|--|
| Propranolol GIK ^a | ↓ Small increase | ↓ No | ↓ ↓ | ↓ No | Yes Yes | Yes No data | Redistrib- Increases or outflow man |
| Nitrates | No | ↓ | No | ↓ | No data | No data | Yes |
| Hyaluronidase ^d | No | No | No | No | No data | No data | Yes |

References

= 51 1.5 140 14° 209 = 60 159 163 167 180 = 50 194 197 = 206 207 208

nally drew attention to the beneficial hemodynamic effects of afterload reduction in patients with left ventricular failure and acute myocardial infarction¹⁹⁹ Experimentally nitroprusside is more potent than nitroglycerin in decreasing systemic arterial pressure but less potent in increasing collateral flow as assessed by the retrograde blood flow method²⁰⁰ while nitroprusside actually reduced collateral flow as assessed by microspheres²⁰⁰ The effects of nitroprusside on ST segment changes are controversial both in animals and in man (see Table I) unfavorable effects may reflect excess hypotension with reduction of post stenotic coronary flow (Table I including Ref 244) In patients nitroprusside is more effective than intravenous nitroglycerin in reducing the peripheral vascular resistance¹ and hence would probably be the agent of choice in a hypertensive crisis complicating acute myocardial infarction However the balance of experimental evidence suggests that nitrates are more effective than nitroprusside in maintaining flow to the ischemic myocardium²⁰¹ The comparable effects of nitroprusside and nitroglycerin on infarct size in patients with predominant arterial hypertension and infarction requires assessment

Nitrates claims and counterclaims Present evidence suggests that oral or sublingual nitrates are a desirable therapeutic agent to reduce myocardial ischemic damage in the presence of left ventricular failure or possibly hypertension In patients without severe left heart failure hypotension tachycardia and even bradycardia are possible and unpredictable side effects with sublingual nitroglycerin²⁰² the addition of phenylephrine to avoid hypertension in patients with

out heart failure is disputed¹⁹³ Such harmful effects have not been reported with intravenous nitrates which can be given even in the absence of left ventricular failure¹⁹³ but require careful hemodynamic monitoring Thusfar sublingual nitrates have been reported to have only beneficial effects when given to patients with severe left ventricular failure or pulmonary edema¹⁹³ However much more knowledge is required about the effects of nitrates on indices of infarct size and mortality as opposed to effects on ischemic damage (ST elevation) and about the comparative effects of nitrate and nitroprusside therapy in patients with hypertension

Nitrates Summary Nitrates have a therapeutic action reduction of preload coronary vasodilation and afterload reduction Substantial hemodynamic evidence shows the benefit of nitrates including sublingual nitroglycerin in patients with acute myocardial infarction complicated by left heart failure but controversy surrounds the use of sublingual nitrates in patients without evident left ventricular failure In comparison with nitroprusside nitrates cause a greater reduction of the preload and a more consistent increase of collateral flow to the ischemic zone but a lesser effect in afterload reduction Critical appraisal showing an effect of nitrates in reducing infarct size in patients are not yet available

4 Increased diffusion to ischemic zone by hyaluronidase

Hyaluronidase was one of the first agents described as improving the consequences of coronary artery occlusion²⁰³ but its mode of action by improving collateral flow is still to be presumed Its introduction into clinical therapy

amelioration of anginal pain but to reduction of myocardial infarct size

Recent evidence supports the hypothesis that nitroglycerin acts as a true coronary vasodilator in dog preparations. Becker and colleagues¹⁸ found a favorable redistribution of coronary flow to the more ischemic subendocardial regions. Epstein's group¹⁹ have shown that when nitroglycerin is given with methoxamine²⁰ to keep heart rate and mean arterial pressure constant then the collateral flow is substantially increased while Bache²¹ found that nitroglycerin infusion could increase blood flow to the central ischemic zone but could not exclude a primary effect on the transmural pressure.

Nitroglycerin and acute ischemic injury. The work of Epstein and co-workers¹⁹ has shown that sublingual nitroglycerin when given to selected patients with acute myocardial infarction may reduce precordial ST elevation. However sublingual nitroglycerin can in some patients cause a serious fall in the arterial pressure²² and the resultant reflex tachycardia could theoretically increase ST elevation. These effects can largely be avoided by limiting the use of sublingual nitrates to patients with left heart failure.²³ Thus in acute pulmonary edema repetitive sublingual nitroglycerin was strikingly effective when employed as sole therapy,²⁴ emphasizing that although nitroglycerin reduces the afterload a more significant effect is reduction of the pre-load.²⁵ Although the simultaneous administration of an α stimulant such as phenylephrine is claimed to reduce the harmful side effects of nitroglycerin in patients without left ventricular failure,²⁶ others find that added phenylephrine is harmful.²⁷ Hence sublingual nitrates should be restricted to those patients with left ventricular failure in whom the prime aim of therapy is relief of failure and in whom reduction of infarct size is only a secondary aim.

But nitroglycerin by infusion reduces the arterial pressure without a tachycardia but with a decreased left ventricular filling pressure and decreased precordial ST elevation.²⁸ These beneficial effects were also evident in patients without left ventricular failure suggesting that intravenous nitroglycerin is a more desirable agent than the sublingual form for the reduction of ischemic injury possibly because the intravenous route allows finer regulation of hemodynamic effects.

Another promising route of administration of nitroglycerin is percutaneously. A theoretical advantage of the ointment would be that if the blood pressure fell too much the agent could simply be wiped off the chest. This simple procedure must merit intensive investigation in acute myocardial infarction.

Nitroglycerin and infarct size. Thus far neither experimental nor clinical studies have been reported on the effect of nitroglycerin on infarct size. But in dogs given both nitroglycerin infusion and methoxamine (to prevent hypotension and tachycardia), creatine kinase depletion decreased.²⁹ A preliminary clinical report suggests that an infusion of nitroglycerin at 50 $\mu\text{g}/\text{minute}$ could limit R wave fall and decrease mortality rate.

Long acting nitrates. Long acting nitrates have for long been thought to have no special advantage over the sublingual nitrate in the treatment of angina. Recently the drug isosorbide dinitrate has been studied in patients with acute myocardial infarction.³⁰ An immediate dose of 10 mg orally was followed by 20 mg 1 hour later. Left ventricular filling pressure fell, but in those patients who had no left ventricular failure the cardiac output stayed the same or fell whereas in those patients with left ventricular failure (defined as a left ventricular filling pressure exceeding 20 mm. Hg) the cardiac output usually rose. The effects were noted up to 9 hours after the control observation i.e. up to 8 hours after the second dose of isosorbide dinitrate. These workers did not assess infarct size but the hemodynamic changes reported for patients with left ventricular failure are those which could be expected to improve ischemic injury.

Nitrates and coronary vasospasm. Maseri and associates³¹ have proposed an important role for coronary vasospasm in the production of angina. One recent report³² suggests that arterial spasm is present in nearly half the patients studied within 12 hours of the onset of symptoms of myocardial infarction. Nitrates relieved the coronary vasospasm which is a further argument for the evaluation of nitrates as anti-infarct agents. For relief of vasospasm nitrates would require comparison with α blocking agents³³ and calcium antagonists.³⁴

Nitrates versus nitroprusside. The effects of nitrates may be compared with those of nitroprusside, the agent used in the work which origi-

Table VI Effect of four anti infarct agents on various stages of experimental myocardial infarction

| | Ischemic injury (ST elevation) | Necrosis (Q formation or histology) | Wound healing |
|---------------|-----------------------------------|---|------------------|
| Propranolol | Yes | Yes | No data |
| GIK | Yes | Yes ²² | Conflicting data |
| Nitrates | Yes | Preliminary data ²² | No data |
| Hyaluronidase | No data | Yes ²² | Yes |

In patients the comparative efficacy of the four anti infarct agents can be assessed by their effects on pain relief the precordial electrocardiogram (ST-elevation or Q formation), mortality rate and long term post infarct prognosis (Table VII) β blockade is effective against the widest spectrum of features of acute myocardial infarction only effects on Q wave formation have not yet been shown (no data)

It is very important to note that only β blockade has thus far been shown to influence mortality rate in patients with acute myocardial infarction and that the only data available are for propranolol given in specific circumstances (given to patients with initial heart rate exceeding 100 beats per minute within a median value of 3 hours of onset see Barber et al²³) Although there are strongly suggestive data for GIK²² a randomized study is essential The general lack of data on the effects of anti infarct agents on mortality rate is not because such effects could not be expected but probably because of the large numbers of patients required to show reduced mortality rate

Harmful effects and contraindications Among the possible harmful effects of anti infarct agents are the provocation of heart failure hypotension tachycardia or fluid and electrolyte problems (Table VIII) Judged by these criteria hyaluronidase is the safest agent followed by GIK Any adverse effects of GIK should be greatly limited by modern technology which can give a bedside glucose and potassium reading within minutes Oral nitrates can cause hypotension and tachycardia β blockade can cause heart failure hypotension and heart block The exact incidence of these side effects will only become known in time but careful patient selection should minimize undesirable effects In selected conditions either nitrates or β blockade are safe the effects of combinations are unknown

although the opposing effects on the heart may suggest the possibility of therapeutic combination

Thus, after due consideration of the contraindications β blockade can be used intravenously in a coronary care unit with appropriate monitoring (oscilloscope and some would say a Swan-Ganz catheter) provided that the drug is given slowly β blockade can be given orally in the hospital outside of the coronary care unit The use of GIK requires monitoring of blood glucose and potassium values which can be done not only in a coronary care unit but also in the general hospital setting The use of nitrates also requires hemodynamic monitoring in the coronary care unit However long acting oral nitrates could be given to patients in the general hospital if heart failure were present Although hyaluronidase may appear to be an agent safe enough for use in the coronary care unit or in the general hospital even outside the hospital it is stressed that the use of anti infarct agents by physicians seeing a patient outside the hospital still requires clinical trial

6 Ideal heart rate and blood pressure

It is sometimes inferred that ischemic damage has extended or regressed by measurements of determinants of the myocardial oxygen uptake The argument is as follows If the afterload reduced oxygen uptake will fall and ischemic injury will decrease Supposing that an intervention reduces the blood pressure from 160 to 110 mm Hg systolic and the heart rate from 110 to 60 beats per minute then the double product is halved the myocardial oxygen demand may be halved and one could infer that there should be substantial reduction in ischemic injury hence in the ultimate infarct size provided that all other factors are equal

As far as heart rate is concerned this argument

tics stems from the experimental observations of Maroko's group^{2, 3, 4} who have shown that hyaluronidase can reduce infarct size and can counteract the development of the Q wave in dogs with coronary ligation. Unexpectedly hyaluronidase is not effective in the pig model⁵ which presumably reflects the necessity for a patent collateral circulation for the action of an anti infarct agent to be manifest.⁶ The pig is thought to have a poorly developed collateral circulation.

Hyaluronidase is one of the few agents which has been shown to counter the electrocardiographic signs of necrosis in patients with anterior myocardial infarction of less than 8 hours duration by inhibition of loss of the R wave and formation of the Q wave. In that study⁷ hyaluronidase was given as 500 units/kilogram intravenously as a bolus every 6 hours for 48 hours. After a negative intradermal test (100 units intradermally observed for 5 minutes) 46 treated patients were compared with 45 control patients. Nine patients were excluded because of an allergic reaction i.e. 9/100 or 9% of patients. Patients with QRS prolongation or left anterior hemiblock were excluded not because it was feared that hyaluronidase could adversely influence such cases but because the assessment of the ECG signs of evolving infarction might have been obscured. If the effect of hyaluronidase on necrosis could be extrapolated from the changes induced in the QRS pattern of the precordial electrocardiogram as in the case of dogs with coronary occlusion⁸ then the degree of reduction of necrosis by hyaluronidase was about 24% (comparing the evolution of ST over 7 days in control with treated patients). This may be considered disappointing compared with the 45% reduction of necrosis in dogs achieved by hyaluronidase.⁹ The difference could be explained by the fact that some of the patients in the hyaluronidase trial probably did not have an adequate coronary collateral circulation and therefore would be less responsive to therapy.

However the above study does not allow the firm recommendation to be made that hyaluronidase should be given to all patients seen early enough in the acute stage of myocardial infarction. A further trial including those patients whose ECG changes did not allow them to be included in the first trial (e.g. patients with posterior infarction) with long term follow up is required before such a conclusion can be made.

Mode of action of hyaluronidase Hyaluronidase increases coronary collateral flow¹⁰ prevents the reduction of coronary flow induced by ischemia and counteracts the formation of edema fluid as ischemia progresses.¹¹ It would seem that the combinations of hyaluronidase with other anti infarct measures warrants experimental assessment.

Hyaluronidase Summary Hyaluronidase has been carefully studied in a wide range of experimental preparations and has been shown to reduce ECG features of necrosis in selected patients with acute myocardial infarction. Thus far no undesirable side effects have been reported except for allergy. Further clinical trials are required before a general recommendation for use of this agent can be made.

5 Comparative effects of the four selected antiinfarct agents (Table V)

Mechanism of action The comparative mechanism of action of the four anti infarct agents selected in this review are shown in Table V. Of the agents β blockade is the only one acting on all the following parameters: heart rate, blood pressure, contractility, metabolism and coronary blood flow. In addition propranolol decreases microvascular damage.¹² GIK improves the metabolism and in doses giving marked hyperglycemia increases indices of contractility while not extending infarct size. Nitrates act chiefly by decreasing the load but also by a blood flow effect. Hyaluronidase is the only agent with no known effect on the mechanical behavior of the heart. Hyaluronidase¹³ is thought to act by improved blood flow and only secondarily by improved tissue metabolism.

The four agents considered act differently on the three stages of development of the experimental infarct: ischemic injury, development of necrosis and wound healing (Table VI). All agents are effective against early ischemic injury as judged by effects on the degree of ST elevation on the epicardial electrocardiogram. All agents are effective against necrosis as judged by Q wave formation on the epicardial ECG or by histology: only hyaluronidase¹⁴ and possibly GIK have been shown to accelerate wound healing¹⁵ (but see Ahmed et al.¹⁶). These experimental criteria do not allow conclusions as to which agent would be the most effective in limiting ultimate infarct size.

approximations of changes in ischemic injury. For more precise evaluations of the effects of anti-infarct agents, measurements of precordial ECG changes or enzyme release patterns would be required.

7 Timing of intervention

A further critical point is to know when to intervene. Table IX shows that some interventions can be effective as judged by ST segment criteria up to 72 hours after coronary occlusion or the onset of symptoms. Most animal work has been done within hours of the onset of coronary occlusion, with the exception of exaggeration of enzyme release by isoproterenol.¹¹ However, the interpretation of those data based on increased liberation of creatine kinase up to 72 hours after coronary occlusion in dogs must be regarded with some reserve because of the capacity of excess β stimulation to cause release of enzymes even from an apparently normal heart.¹⁴ Nevertheless, Shillingford and his group¹⁵ found that β blocking agents could decrease ST-elevation up to 72 hours after the onset of symptoms in patients with myocardial infarction (Table IX), suggesting a prolonged effect of β stimulation. Increased urine catecholamine secretion values are found up to 4 days after the onset of symptoms in some patients.¹ Pelides and associates¹⁶ restudied three patients at increasing times after the onset of symptoms and although there was a decreasing effect at the second study, nevertheless they still obtained a decreased ST elevation and decreased precordial area of ST elevation.

However, chronic therapy (started before the infarct developed) with β blockade in patients with acute infarction can decrease ST elevation without altering the rate of Q wave formation.¹

Some of the above data suggest that it would seem reasonable to intervene with β blockade up to 72 hours or with afterload reduction (nitrates, trimethaphan) 8 to 14 hours after the onset of symptoms. On the other hand, the data showing favorable electrocardiographic effects on necrosis (assessed by QRS changes) of hyaluronidase in patients were obtained within 8 hours after the onset (mean 4.6 hours). An important finding with hyaluronidase (given to dogs as a single bolus) was that it had to be given within 6 hours after experimental coronary occlusion and it had no effect 9 hours after coronary occlusion.¹⁷

Similarly, propranolol had to be given within 4 hours of the onset of symptoms to be effective in reducing enzyme release.¹⁸ Practolol was given within 3 hours (median) of onset of symptoms.¹⁹ Barber and co-workers¹⁸ Selwyn and associates¹⁹ studied the rate of evolution of Q wave changes and found that complete development took 6 to 12 hours. Thus, from many points of view, interventions should ideally start within 6 hours of the onset of symptoms.

Conclusions There is no unanimity on the timing of the interventions. Some data suggest that anti-infarct agents could be given 2 to 4 hours after the onset of symptoms. Clearly, however, the sooner after the onset of symptoms the therapy is given, the better. Data with propranolol and hyaluronidase suggest that a delay of 4 to 8 hours (respectively) is the maximum that can be tolerated.

8 Anticipated effects of commonly used agents on ischemic injury of infarct size in patients

Among agents frequently used in the therapy of acute myocardial infarction are heparin, an oxygen mask, antiarrhythmic agents such as lidocaine and anti-failure drugs such as digitalis, diuretics and aminophylline, and agents against pain such as morphine. It may be that each of these agents may influence ischemic injury of the infarct size.

Heparin is frequently used in acute myocardial infarction for its supposed effects in preventing venous thrombosis and possibly in stopping the formation of arterial thrombosis. The latter action has not been well documented but would be logical if the actual coronary thrombosis (when present) has a stuttering or delayed onset as originally suggested by clinical work and recently confirmed experimentally.² Heparin decreases signs of ischemic injury and lessens the necrosis when given following coronary artery ligation in the dog and decreases ST segment elevation in patients.¹⁶ Hence it would be logical to test the effect on infarct size. However, a cautionary note is needed. Since heparin increases blood free fatty acids, this action must be expected to antagonize the antithrombotic and platelet effects of heparin.

Increased arterial oxygen receives support for its use because on 100% oxygen patients experienced decreased precordial ST segmental

Table VII Effect of four anti infarct agents on the features of acute myocardial infarction in man

| | Pain | ST-elevation | Q formation | CK infarct size | Mortality | Post infarct prognosis |
|----------------------------|----------------------|--------------|----------------------|----------------------|------------------|------------------------|
| β blockade | | | | | | |
| i Propranolol | Yes | Yes | — | Yes | — | — |
| ii Practolol | Yes | Yes | — | — | Yes | Yes |
| iii Metoprolol | Yes | Yes | — | — | — | — |
| GIK | — | Yes | — | No | Suggestive data | — |
| Nitrates | Yes (preliminary) | Yes | Yes (preliminary) | Yes (preliminary) | Preliminary data | — |
| Hyaluronidase ¹ | — | — | Yes | — | — | — |

add n death ex l dng inferior infarct mechanism prob bly does not in oliv early anti infarct effect because practol i started after the acute phase myocardial infarction Note that oral practolol is not a ge v labl

CK infarct size = either rat of release of creatine kinase or actual calculation of inf t e "

i = absence of d ta
references

51 140 145 = 148 147 148 235 = 235 = 157 165 1 0 180 = 190 196, 259 260 = 306

appears to be valid In closed chest dogs the severity of ischemic injury as judged by ST elevation was directly related to the heart rate over the range 30 to 215 beats per minute⁷ whereas an increased heart rate induced by atrial pacing increased estimated infarct size in dogs by 70%⁷ (For the possible effects of atropine in avoiding the dangers of bradyarrhythmias see section 8)

However as far as blood pressure is concerned the oxygen sparing effect of hypotension induced by hemorrhage appears to be outweighed by the harmful effects of decreased coronary perfusion pressure¹⁸ Hence it would follow that hypotension plus bradycardia requires atropine treatment but bradycardia without hypotension or heart block does not require therapy The ideal hypotensive agents should therefore be those that at the same time will decrease arterial pressure but also protect the ischemic myocardium from underperfusion Both β blockade and nitrates may do this by redistribution of blood flow and vasodilation respectively Conversely an increased blood pressure increases ischemic injury and infarct size Even systolic blood pressures of 150 to 165 mm Hg gave rise to infarcts about one quarter larger than did pressures reduced by about 30 to 40 mm Hg⁷ although the use of computer predicted infarct sizes is open to some question

The ideal blood pressure in acute myocardial infarction has not been determined but in the case of patients treated by intravenous propranolol¹⁹

the blood pressure could be reduced from an initial mean arterial pressure of 92 to only 76 mm Hg Similarly intravenous nitroglycerin could reduce blood pressure from a mean of 108 to 87 mm Hg¹⁹ while ST segment elevation decreased Thus it seems as if patients with acute myocardial infarction can tolerate relatively low heart rates and blood pressures and that such values may beneficially influence ischemic injury and infarct size However blood pressure reduction achieved by agents such as nitroprusside and diazoxide which do not at the same time increase collateral flow need not always be beneficial but may be harmful^{20 21}

The effects of increases in heart rate or blood pressure have been compared in patients with fixed coronary obstruction²² Tachycardia was more harmful than hypertension as judged by increased chest pain and ST segment changes despite similar increases in myocardial oxygen consumption In the case of metabolically active agents such as GIK the heart rate and blood pressure cannot be used to assess any oxygen sparing effect nor can any metabolic effect of β blockade thus be assessed Nor can the effects of complex interactions in patients with left ventricular failure and/or dilated hearts be so assessed Indirect estimates of hemodynamic performance also give no idea of the effects of hyaluronidase which does not influence hemodynamic parameters Thus at present changes in the inferred indices of myocardial oxygen demand (heart rate blood pressure) can only give rough

Table IX Period of delay from onset of symptoms or coronary occlusion to intervention changing ischemic damage or infarct size

| Intervention | Period | Conditions |
|--|-----------------------------------|---|
| A. Decreasing ischemic damage | | |
| Nitroglycerin (IV) | Up to 111 hours (mean 8 hours) | After onset of symptoms in patients ST-elev |
| Practolol (IV) | 5-72 hours (mean 31 hours) | Effect on precordial ST-elevation in patients |
| Practolol (IV) ^a | 24-72 hours | Effect on pain in patients with acute myocardial infarction |
| B. Decreasing infarct size | | |
| Hyaluronidase | 6 hours (9 hrs no effect) | Coronary occlusion in dogs |
| Propranolol | 3 hours | Coronary occlusion in dogs |
| Propranolol | 4 hours | Enzyme release in patients |
| GIK and propranolol ^a | 3 hours | Coronary occlusion in dogs |
| Afterload reduction ^a (trimethaphan) | 14 hours | After onset of symptoms in patients |
| C. Increasing infarct size | | |
| Isoprenalol | 72 hours | Closed-chest dogs enzyme release |
| Digitalis | 11-19 hours | After onset of symptoms enzyme release |

^a A ganglion blocking agent

IV = intravenous administration

tion relief of pain and pulmonary edema should lead to decreased discharge of catecholamines.²⁰⁰ Although the possibility that morphine could cause arterial hypotension in some patients raises doubts about coronary perfusion, the hypotensive effect appeared short lived and 15 minutes after the morphine baseline arterial values were regained.²

Atropine when given for bradycardia, may avoid bradyarrhythmias which could increase infarct size by hypoperfusion. On the other hand an atropine induced tachycardia could also increase infarct size. The optimal lower limit of heart rate has not yet been defined.

Commonly used agents. Summary. It is reassuring that many agents routinely used in the management of acute myocardial infarction are more likely to limit than to extend infarct size or ischemic injury with the exception of digitalis given to the nonfailing heart. Aminophylline is probably harmful by provocation of arrhythmias.

9. Can provisional guidelines to management of infarct size be given?

A distinction must be made between a general recommendation and the time has not yet come to introduce anti-infarct agents into general cardiological practice and recommendations for

individual patients. General recommendations could only be made once randomized trials have shown that relatively safe agents could decrease mortality rate or significantly change other complications of infarction. That point has not been reached. In the meantime the cardiologist faced with a patient with myocardial infarction tries to match existing data with the desire to do the best for the individual patient.

Because it has been shown that larger infarcts are on the whole associated with a worse prognosis it would seem only prudent to avoid agents known or suspected of increasing myocardial infarct size. The major agent is isoprenaline.

Secondly when complications call for treatment those agents should be used which are thought to reduce infarct size everything else being equal. For example if load reduction is required in the presence of left ventricular failure then currently available literature would suggest a role for nitrates (especially long acting compounds) to reduce the preload (and possibly the afterload).

Thirdly when there is clinical or laboratory evidence of reinfarction or extension of the infarction process the case for therapeutic intervention becomes stronger.

Each agent has some arguments for a specific use. Thus β blockade may be indicated for

Table VIII Possible harmful side effects of four anti infarct agents

| | Heart failure | Hypotension | Bradycardia | Heart block | Tachycardia | Fluid and electrolyte problems |
|-------------------|---------------|-------------|------------------|-------------|-------------|--------------------------------|
| β -blockade | Yes | Yes | Yes | Yes | No | No |
| GIH | No | No | No | ? | No | Yes |
| Nitrates | No | Yes | Yes [†] | No | Yes | No |
| Hyaluronidase | No | No | No | No | No | No |

[†] Yes with intravenous nitroglycerin or oral isosorbide dinitrate

Rarely found in presence of LV failure or hypertension

Very rapid glucose and K⁺ measurements now available to avoid excessive hyperglycemia or potassium deviations in blood K⁺

† May prolong conduction time in healthy patients; no specific data on patient with infarction but not reported side effects.

† Seven case reports. † Mechanism unknown

tion.²¹ However the complex hemodynamic effects of oxygen in some patients¹ mean that ischemic damage would not necessarily improve.

Lidocaine although given as an antiarrhythmic agent reduces epicardial ST elevation when given at a dose of 3 mg/kg in dogs with coronary occlusion.²¹ Lidocaine also reduces ischemic damage during cardiopulmonary bypass.²² Lidocaine decreased catecholamine induced enzyme release from the isolated perfused rat heart. Lidocaine also improved myocardial blood flow by 60% in patients studied 15 days after acute myocardial infarction. Thus lidocaine would probably improve ischemic damage but firm data are lacking.

Verapamil is also primarily an antiarrhythmic drug used for supraventricular tachycardia but decreases experimental infarct size²³ possibly by selectively decreasing the contractility of the ischemic zone.²

Disopyramide given orally (100 mg four times daily) as soon as possible after admission to hospital has very recently been reported to limit extension of infarction to decrease serious arrhythmias and to decrease mortality rate.²⁴ The design of this study can be criticized chiefly because the control mortality rate was so high. These observations therefore need confirmation but do suggest the feasibility of more effective therapy for patients not managed in a coronary care unit.

Antiarrhythmic agents may therefore in general be held to have anti ischemic effects. In addition to the effects of lidocaine, verapamil and disopyramide β blockade has antiarrhythmic effects¹ as do nitrates. Glucose insulin potassium is antiarrhythmic in dog infarcts.¹ The mechanisms linking infarct size and arrhyth-

mias are ill understood but it is reasonable to conclude that the use of antiarrhythmic agents will in general reduce infarct size and the use of anti infarct agents will in general reduce arrhythmias because patients with large infarcts also tend to have more arrhythmias.¹

Digitalis as acetyl strophanthidin when given to patients without overt heart failure 11 to 19 hours after the onset of symptoms could greatly increase infarct size as estimated by creatine kinase release curves.²¹ However animal data suggest that digitalis compounds when given in the presence of cardiomegaly could exert a beneficial effect on infarct development probably by reduction of heart size and myocardial oxygen demand.²⁵ In the presence of uncontrolled atrial fibrillation digitalis compounds could also be expected beneficially to influence infarct size by reducing the heart rate. Finally digitalis compounds can limit the depressant effects of β blockade on the ischemic dog myocardium and thereby actually decrease ischemic injury.²⁶

Diuretics should act to reduce infarct size in the presence of left sided failure by reducing the preload and hence the heart size.

Aminophylline may be used in the presence of bronchospasm associated with left ventricular failure. However by inhibition of phosphodiesterase it may increase cardiac cyclic AMP also with an arrhythmogenic effect.²⁷ In critically ill patients there was an inordinately high incidence of cardiac arrest which followed intravenous administration of aminophylline.²⁸ Aminophylline is thus probably too suspect to allow its evaluation in relation to infarct size.

Morphine has not been studied for effects on infarct size. There is some evidence that its effect in pulmonary edema is antiadrenergic²⁹ in addi-

requirement for hemodynamic or metabolic intervention in any given patient could be better assessed

The strongest evidence for the use of anti-infarct agents stems from experience with β blockade but even there there is as yet no evidence that reduction of ischemic injury and enzyme release leads to improved long term prognosis

The short history of the therapeutic approach to myocardial infarction has already seen anti-coagulants and hypocholesterolemic agents running into strong counterarguments. Thus it is prudent to emphasize three major problems

First the hypothesis that a large infarct size is associated with more complications and a higher mortality rate seems acceptable in the light of present evidence^{2, 34} however the converse hypothesis (therapeutically induced decrease of infarct size, fewer complications and lower mortality rate as a result of therapy) still requires proof even though it might seem a self-evident truth

Second the data on patients are scanty especially when it comes to effects on indices of infarct size as opposed to indices of ischemic injury

Third until a rapid on-line method for the assessment of the development of the infarct process becomes available it will be difficult to select a therapy to meet the specific needs of an individual patient

Conclusions In spite of severe reservations about how best to measure or modify infarct size the concept of modification of infarct size has introduced an entirely new dimension into our management of acute myocardial infarction

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Addendum

Since this article was prepared in 1978 two preliminary reports have shown a relation between the use of anti-infarct agents and a reduction in mortality in acute myocardial infarction. An infusion of nitroprusside for 24 hours followed by isosorbide dinitrate for 7 days reduced death and ventricular fibrillation. ¹ GIK

improved mortality in the randomized trial provided that patients with a low cardiac index, high pulmonary artery end diastolic pressure were excluded. Because both nitrates and GIK appear to have antiarrhythmic properties these studies do not prove a protective effect of limitation of infarct size per se. Another study suggests that spasm is not the usual initial event in acute myocardial infarction³⁵ thereby arguing against relief of spasm as a mode of action of nitrates in acute infarction.

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inappropriate tachycardia but proof of the efficacy of agents other than practolol is awaited. In such patients with heart rates over 100 per minute practolol started within a few hours of the onset of symptoms and then continued has been shown to improve the mortality rate up to one year post infarct but prolonged therapy with practolol can no longer be accepted. Some studies¹¹³ and theoretical considerations (Part I of this review) suggest that β blockade could be given to all patients seen early enough and in whom β blockade is not contraindicated provided there is appropriate monitoring in a coronary care unit. Furthermore ideal properties of the β blocker (especially in relation to intrinsic sympathetic activity) remain to be determined. Whether the possible harmful effects (e.g. bradycardia, hypotension and conduction disturbance) would outweigh the beneficial effects would depend on the success of the monitoring procedures. And the possible use of oral β blocking agents other than practolol which is no longer available requires clinical trial. Thus further experiments with other β blocking agents is required before definite guidelines can be formulated in such patients.

GIK may be an inotropic agent which does not extend infarct size. Long acting nitrates are of proven use in selected patients with left ventricular failure complicating acute myocardial infarction but the effects on infarct size are not known. Hyaluronidase may come to be the most suitable nonspecific therapy for patients seen in the early hours of the development of the heart attack. In every case the results of large scale randomized trials with mortality as end point are awaited and such results will affect the recommendations to be made.

Of the agents considered only hyaluronidase and GIK can be given without hemodynamic monitoring in a coronary care unit and GIK requires metabolic monitoring. While it would seem ethically acceptable for the agents discussed to be used in individual patients by physicians who understand the problems involved the benefit remains hidden and only the results of large scale randomized trials could uncover the real benefit there might be. Until a rapid on line method of measuring an index of infarct size is available assessment of the therapeutic requirements of the individual patient will not be clearly defined.

Table X Effect of repetitive intravenous injections of practolol on ST segment elevation (Based on data of Pelides et al.¹¹)

| Patient | Times of study (hr post-onset) | Late effect as % of early effect | |
|---------|--------------------------------|----------------------------------|--------------------------|
| | | % reduction ST area | % reduction ST elevation |
| CN | 18 and 66 hrs | 19% | 33% |
| DW | 14 and 38 hrs | 30% | 3% |
| FF | 27 and 72 hrs | 43% | 48% |

In summary it must be emphasized that the subject is in the early stages of development. The ideal must be to obtain more information on the use of anti infarct agents by rigorously conducted therapeutic trials. It would be especially important to obtain studies on the effect of such agents on short and long term mortality rates and for this multicenter trials would be needed. In the meantime there are arguments for and against each of the four agents here reviewed.

10 What can be hoped for?

Thus far we have information that two anti infarct measures afterload reduction and hyaluronidase decreased indices of infarct size and that the extent of effect was about 25% in patients judged respectively by creatine kinase curves or Q wave effects. Furthermore propranolol decreased creatine kinase release by about 30%.¹¹ Quantification in patients in other cases is not available but a variety of agents decreased measured infarct size by 40% in animals.¹⁰⁰ The difference may well be because only patients with a collateral circulation appear to respond to β blockade¹¹ which could readily be explained by the requirement of a collateral circulation¹² to create a zone of ischemia of lesser severity on which the anti infarct agent should be most active.

If the average infarct were to be reduced by only 25% the effect on mortality rate may well not be striking although even a relatively small reduction in infarct size of every individual treated could make a substantial difference in the cumulative mortality rate of a country like the United States of America where acute myocardial infarction is common. However the effect on the individual patient will generally not be striking unless new techniques are developed to allow more specific monitoring of the rate at which the infarction process unfolds so that the

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Fig. 1 The left ventricular outflow tract of a patient with hypertrophic cardiomyopathy is displayed. The anterior mitral valve leaflet has been reflected. Clinically obstruction was present. Severe endocardial thickening below the aortic valve is present together with two systolic (Zahn-Schmincke) pockets.

Several familial studies have established that hypertrophic cardiomyopathy is a genetically transmitted disease but sporadic occurrence is well recognized.

Historical note

Attention to this condition was drawn by Brock in 1957¹ who illustrated in his report a case of functional obstruction of the left ventricle the patient having been diagnosed clinically as suffering from aortic valve stenosis. At operation the aortic valve was found to be normal and a subaortic muscular bulge of the interventricular septum was noted. The following year the pathology of this condition was detailed. The condition was however recognized in the nineteenth century and Dutrich in 1852 was credited with the first description of this disorder. This credit was misplaced; a Dutrich's patient suffered from fibrous subaortic stenosis. More recently Liouville in 1869 and Hilgerson in 1869 have been credited with the first descriptions of hypertro-

phic cardiomyopathy.^{2,3} As early as 1600, the disease was called left sided muscular cor. stenosis and a disturbance of embryonic growth was suggested as the possible etiology, mechanism.

Since the description in 1956 numerous reports on this condition have appeared in the literature. Great diversity of opinion does exist as to whether or not the appearances are pathognomonic or characteristic or whether the changes are non-specific merely reflecting severe hypertrophy.

The purpose of this review is to critically analyze the various observations that have been reported by numerous workers and to evaluate their findings in order to ascertain whether or not a diagnosis can be achieved pathologically. It is proposed to describe the findings under the following major headings: macroscopic appearances, microscopic appearances, and electron microscopic changes. The description by Teare⁴ will be detailed first, any subsequent additional observations

The pathology of idiopathic hypertrophic subaortic stenosis (hypertrophic cardiomyopathy) A critical review

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Idiopathic hypertrophic subaortic stenosis (IHSS) or hypertrophic cardiomyopathy belongs to the group of diseases designated cardiomyopathy, a term introduced by Brugada in 1957. Older classifications separated primary forms (where the cause of the heart muscle disease was unknown) and secondary forms (where a disease process elsewhere in the body was associated with cardiovascular manifestations). Much confusion about the classification has arisen since that time and it was suggested that cardiomyopathy should be restricted to those entities in which the cause was unknown (the previous primary group) and that secondary cardiomyopathy should be replaced by the term specific heart muscle disease.

Not only has confusion reigned regarding classification but the various types of cardiomyopathy masquerade under several synonyms which for IHSS or hypertrophic cardiomyopathy include functional obstruction of the left ventricle, asymmetrical hypertrophy of the heart, pseudo aortic stenosis produced by ventricular hypertrophy, familial muscular subaortic stenosis, obstructive cardiomyopathy simulating aortic stenosis, idiopathic hypertrophic subaortic stenosis, muscular subaortic stenosis, functional subaortic stenosis, diffuse subvalvular aortic stenosis, muscular subvalvular aortic stenosis, hereditary cardiovascular dysplasia, hypertrophic subvalvular aortic stenosis, subvalvular aortic stenosis of muscular type, idiopathic cardiac hypertrophy simulating valvular heart disease.

ease¹⁶ hypertrophic obstructive cardiomyopathy¹⁷ primary idiopathic myocardial obstructive hypertrophy¹⁸ hypertrophic cardiomyopathy¹⁹ and hypertrophic cardiomyopathy with or without obstruction^{20, 21}. Of these many synonyms the terms idiopathic hypertrophic subaortic stenosis and hypertrophic cardiomyopathy have emerged as those most frequently used throughout the world.

Despite many suggestions of a possible etiology (or etiologies) no cause for hypertrophic cardiomyopathy has so far been firmly established and therefore this entity belongs by definition to this group of cardiac diseases.

The incidence of IHSS is difficult to ascertain in view of the reports having been published from specialized centers. Judging from comparative surveys and personal experience it appears that hypertrophic cardiomyopathy occupies an intermediate position in incidence between the other two types of cardiomyopathy: the dilated (congestive) type on the one hand and the restrictive/obstructive type which is the rarest form on the other.

The earlier British nomenclature (hypertrophic obstructive cardiomyopathy) implied that the obstruction was an essential element of the clinical manifestations. Increased clinical experience has however shown that the obstruction is incidental²² and that the essential hemodynamic abnormality is failure of diastolic compliance.

The disease may affect any age varying from the newborn to old age: the oldest patient reported being 87 years old.²³

Males are more commonly affected than females in some series^{24, 25} but an equal sex incidence has been noted by others.²⁶ In most series the disease is diagnosed in early adult life.

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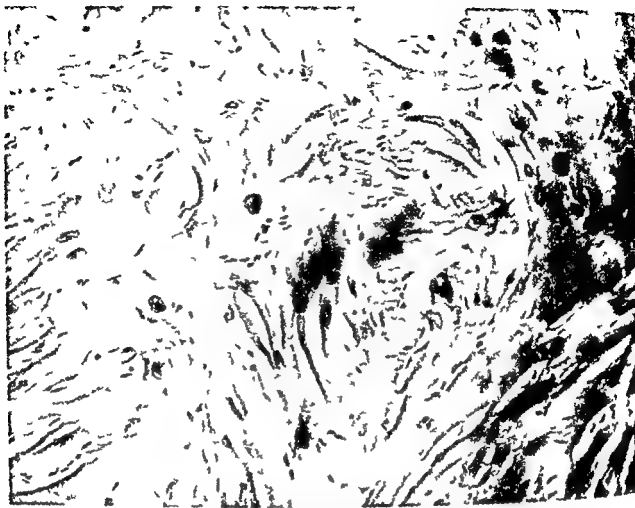


Fig 2 Photomicrograph of the myocardium from the septal region from a patient firmly diagnosed clinically as hypertrophic obstructive cardiomyopathy. Extensive disarray of myocardial fibers and attempts at whorl formation are present. In addition, severe hypertrophy and an increase in collagen tissue interrupting muscle bundles are seen. Nuclear changes are not prominent. Perinuclear halos are absent. Although not all diagnostic criteria are met in this illustration, the combination of the changes present characterizes this condition. Hematoxylin-eosin stain, original magnification $\times 650$.

with congenital heart disease is unreliable. This applied particularly to the situation when marked absolute thickening was absent. In a clinical and echocardiographic follow up study over a period of two years, it has also been shown that resolution of the septal thickening may occur. Asymmetric septal thickening can occur in normal embryonic and fetal hearts as well as in the newborn. Its association with right ventricular congenital anomalies was stressed. Rarely did it accompany abnormalities of left heart development. It was therefore suggested that significant asymmetric hypertrophy in the adult heart and in the proper clinical setting can be a valuable diagnostic clue to the presence of hypertrophic cardiomyopathy.

Analyzing these various points, there is fairly uniform agreement that on a degree of asym-

metric septal thickening are non specific. A severe degree of asymmetric septal thickening in combination with right ventricular congenital anomalies is also not a reliable feature of associated hypertrophic cardiomyopathy. Absolute septal asymmetric hypertrophy, even when associated with left sided cardiac anomalies, is not suggestive of cardiomyopathy. In any event, caution must be exercised in interpreting this finding and confirmatory histologic examination should always be sought.

Hypertrophic cardiomyopathy has been noted to occur in a variety of other cardiovascular abnormalities such as lentiginosis, congenital arterial disease, Turner's syndrome, hyperthyroidism, isolated dextroversion, and Friedrich's ataxia.¹⁰ Unless other evidence indicates the presence of asymmetric hypertrophy of the

tions that have been made will then be detailed and each section will be summarized separately in the light of the more recent findings

Macroscopic appearances

Asymmetric hypertrophy of the interventricular septum is striking on naked eye examination and consists of a localized and diffuse hypertrophy of the interventricular septum disproportionate to the rest of the left ventricle. The prominent bulge towards the mitral valve was emphasized.

The asymmetric hypertrophy of the septum has been consistently confirmed.

Additional descriptive features included simulation of watered silk of the interventricular septum when the ventricles had been transected.¹⁰ Endocardial thickening of the outflow portion of the interventricular septum occasioned by the impact of the anterior mitral valve leaflet, the so-called mirror image of the leaflet had also been noted. A heart showing endocardial thickening is illustrated in Fig 1. Abnormalities of the positioning of the anterior mitral valve leaflet have also been recorded. Instead of the normal insertion of the anterior mitral valve leaflet to the base of right aortic valve leaflet in this condition insertion below the posterior aortic valve cusp was noted in two patients. Thickening of the mitral valve in cases of mitral insufficiency has been observed in over half the patients. In the various descriptions, cavity obliteration resulting in a small ventricular cavity has been frequently noted but this is not necessarily always present.¹¹ The normality of the coronary arteries has often been stressed.

Measurements of the interventricular septum have indicated that values greater than unity are found when the ratio of the thickness of the interventricular septum and the free left ventricular wall is calculated. Echocardiographic identification of asymmetric septal hypertrophy has also been undertaken¹² and a ratio of ventricular septum to posterior left ventricular free wall was 1.03 in normal individuals and in patients with fixed left ventricular obstruction and in patients suffering from miscellaneous cardiovascular diseases. By contrast in patients with hypertrophic cardiomyopathy the ratio exceeded 1.3 in every case.

Asymmetric hypertrophy of the interventricular septum at macroscopic level was therefore

Table 1 Histochemical investigations

| Substance |
|---|
| Glycogen |
| Neutral fat |
| Lipofuscin |
| Dehydrogenases |
| Reduced nicotinamide adenine dinucleotide dehydrogenase (NADH D) |
| Reduced nicotinamide adenine dinucleotide phosphate dehydrogenase (NADPH D) |
| Succinate dehydrogenase |
| Lactate dehydrogenase |
| Isocitrate dehydrogenase |
| β hydroxybutyrate dehydrogenase |
| Oxidases |
| Monoamine oxidase |
| Cytochrome oxidase |
| DOPA-oxidase |
| Lysosomal and other hydrolases |
| Non specific esterase |
| indoxyl |
| α naphthyl |
| Acid phosphatase |
| Cholinesterase |
| Alkaline phosphatase |
| Adenosine triphosphatase |
| Phosphorylase |
| Leucine aminopeptidase |

Methods were carried out routinely the others occasionally

considered pathognomonic of hypertrophic cardiomyopathy. More recently doubt has been cast on the reliability of this finding when observed alone or in combination with other anomalies of the heart. Thus asymmetric septal thickening has been found in normal developing hearts and in association with congenital heart disease and other cardiac conditions.¹³⁻¹⁶ In a study of eight cases with asymmetric hypertrophy further histologic examination has shown characteristic features of hypertrophic cardiomyopathy in only two of the eight cases. Because of these findings and as a result of another study¹⁰ it was concluded that disproportionate ventricular septal thickening in association with other cardiac diseases may be due to secondary hypertrophy and may not represent genetically transmitted asymmetric hypertrophy.

In a study of 125 infants two years of age or less, interventricular septal to left ventricular free wall thickness ratios of 1.2 or more were found in 25% of cases. Using histologic hypertrophy as the sole criterion for associated hypertrophic cardiomyopathy

3 Fibrosis

4 Degenerating muscle with disappearing myofibrils

5 Disorganized whorling muscle

In a longitudinal section the maximum points that could be obtained were 15. This was expressed as 100%.

The material had been obtained at surgery where removal of muscle formed part of the operative procedure. Comparison with tissue from similar sites also obtained by surgery from patients suffering from tetralogy of Fallot, subaortic stenosis, ventricular septal defects and mitral valve disease as well as patients with congestive cardiomyopathy was undertaken. At the histologic level in just over one half of the patients with hypertrophic cardiomyopathy an index of over 65% was obtained permitting a diagnosis of that condition. In the remaining patients overlap between those clinically diagnosed as suffering from hypertrophic cardiomyopathy and the tissue used for comparison existed.

Extensive additional *histochemical investigation* had also been undertaken which is summarized in Table I. Of the large number of enzymes investigated that of glycogen particularly pooling in the perinuclear areas was helpful in distinguishing hypertrophic cardiomyopathy from hypertrophy of the myocardium due to other causes. This finding increased the diagnostic reliability considerably.

The morphologic characteristics have not only been confirmed by most workers cited but also by others.²²

The specificity of disarray has however been questioned. Disarray is found in hearts at the junction of the interventricular septum with the ventricular free walls in congenital heart disease including semilunar valve atresia with intact ventricular septae and tetralogy of Fallot. It has also been observed in acquired heart conditions such as systemic hypertension and coronary artery disease. Some disarray was also noted in normal hearts but not in the myocardium of developing embryos and fetuses despite disproportionate septal thickness. Irregular arrangement of myocardial fibers was also not marked in left ventricular myocardium.

Therefore neither hypertrophy alone nor fiber disarray alone nor the combination of both these features in the myocardium could be considered pathognomonic of hypertrophic cardiomyopathy.

athy.²³ In the study of patients with coronary heart disease, systemic hypertension, coronary heart disease and patients with cor pulmonale, disarray of myocardial fibers to a mild degree was noted in all cases. The extent of fiber disarray in individual hearts varied considerably but involved less than 11% of the myocardium and never more than 20%. Comparison with a case with hypertrophic cardiomyopathy showed more than 50% of the myocardium was involved not only in the septum but also in the walls.

A quantitative analysis of disorganized cardiac muscle cells in the ventricular septum has recently been undertaken.²⁴ In hypertrophic cardiomyopathy septal disorganization was found at necropsy in 94% of the 54 patients studied. Disorganization was extensive in most of the patients involving at least five % or more in 4 of the sections examined and 25% or more of 1 sections in 56% of cases. Septal disorganization to a limited extent was present in only 9% of 1 control patients (patients with other heart diseases or with normal hearts). In only 10 percent did the abnormally arranged myocardial fibers occupy five % or more of the tissue section. This study has shown that widespread ventricular septal disorganization of myocardial fibers though not pathognomonic of hypertrophic cardiomyopathy is a very sensitive and a specific histologic marker for this disease.

Analyzing the various observations that have been made at the histologic level there is ample evidence that individual histologic changes are consistently found in hypertrophy, other than that of hypertrophic cardiomyopathy (see for example Figs 3c and 4b of reference 33). Despite the unequ shoreable disarray these changes should not in my opinion be interpreted as representing hypertrophic cardiomyopathy. Apart from disarray other accompanying changes such as extreme hypertrophy of fibers, bizarre nuclei, perinuclear halos and increased collagen tissue are essential for verification of the diagnosis particularly when widely distributed in the tissue sections. The presence of pools of glycogen increases the diagnostic reliability.

Electron microscopic changes

Disarray of myocardial fibrils coursing in opposite directions were noted at this level of investigation (Fig 3). In addition fibrillar defects



Fig 3 Electron micrograph showing disarray of myocardial fibrils and widening of Z bands. (Lead citrate and uranyl acetate original magnification $\times 38,400$)

septum cannot be used as a firm diagnostic parameter in these associated conditions

Microscopic appearances

Bizarre arrangement of bundles of myocardial fibers running in diverse directions and separated by connective tissue and clefts were noted. The connective tissue was found to interrupt the muscle bundles. The thickness of myocardial fibers varied and the clefts were lined by endothelial cells and covered by sparse elastic tissue resembling normal endocardium. In some cases these clefts communicated with the cavity of both ventricles but as they pursued a muscle bound course functional shift of blood from one ventricle to the other was considered unlikely.

In the original description thickening of the mitral valve was not emphasized. Subsequently non specific thickening due to superimposition of collagen tissue on atrial surfaces of the mitral valve leaflets due to mitral insufficiency was observed in approximately half the patients.⁶

Disarray of myocardial fibers has been confirmed^{1, 2, 3, 4, 5} and was considered to be the most characteristic feature. Severe hypertro-

phy with individual myocardial fibers measuring up to 100 microns in diameter has been observed. The presence of clefts has also been reconfirmed not only in the myocardium⁴ but also in the conducting system.³ Their significance is not fully understood as they have not been consistently found. Their non specificity was emphasized.^{6, 4}

Other additional fiber alterations have been noted which consist of degenerating myocardial fibrils and the appearance of perinuclear halos as well as a whorled arrangement of myocardial fibers⁶ (Fig 2). Changes in the intramural arterioles and small arteries showing medial thickening and cellular intimal proliferation have also been observed.^{3, 4, 5} These changes were usually mild not resulting in narrowing of the lumen of more than 50%.⁶

In an attempt to quantify various histologic parameters an index (the histologic HOCM index) was devised. Points from zero to three for each of the following changes were evaluated:

- 1 Short runs of fibers interrupted by connective tissue
- 2 Large bizarre nuclei

changes is equally reliable. If biopsy material permits only one method of analysis that of histology is preferable to ultrastructural or histochemical evaluation. It should be remembered that any individual histologic feature is unreliable. It is the combination of changes that characterize and may indeed be considered pathognomonic of hypertrophic cardiomyopathy.

This review has concentrated on the morphologic aspects but it is clear that examination cannot and should not be undertaken without full knowledge of the clinical details. Despite the extensive work that has been detailed in this communication there is still further need to define even more precisely the morphologic characterization as well as the clinicopathologic correlation of hypertrophic cardiomyopathy. If all these factors are combined the problem as to whether an individual patient does or does not suffer from hypertrophic cardiomyopathy can then be fully solved.

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tion focal mitochondrial accumulation (the so called mitochondriosis) varying degrees of mitochondrial damage and increased number of lysosomes and lipofuchsin granules together with swelling of the sarcotubular system were noted. Comparison with tissue obtained from cases with other conditions resulting in hypertrophy was also made. Analysis of seven electron microscopic features showed that extensive overlap between those patients with hypertrophic cardiomyopathy and the control cases existed.

By contrast other workers considered disarray of myocardial fibrils which did not occur necessarily in all cells together with abnormally arranged myofibrils, abnormal intercellular junctions and abnormalities of Z bands as constituting distinctive changes. Minor abnormalities of myofibrillar disorganization were however noted in three out of 31 patients with congestive cardiomyopathy.¹⁸ Disorganization of myofibrils and other abnormal features have been widely confirmed.^{14, 17}

Overlap between hypertrophic cardiomyopathy and other conditions resulting in hypertrophy of the myocardium⁴ has been confirmed by others.^{1, 8, 19} Indeed it has been suggested that intracellular disarray was more frequent in acquired heart disease than in hypertrophic cardiomyopathy. Irregularly arranged myocardial fibrils have also been observed in the zones adjacent to experimental myocardial infarction²⁰ and in embryonic heart muscle.²

Analyzing the reports on electron microscopic findings it has become clear that the features of hypertrophic cardiomyopathy can be extensively mimicked by other cardiac conditions which result in hypertrophy. If however intra and interfibrillar disarray is extensive the changes are suggestive but not pathognomonic of hypertrophic cardiomyopathy.

So far distinction between two clinical groups recognized for several years has not been made. In one group obstruction of the outflow of blood from the left ventricle (or right or both ventricles) played a significant role in the clinical symptomatology. In the other group of patients obstruction has never been clinically manifest. Macroscopic studies have shown non uniform distribution of free wall thickening but a normal posterobasal region in non obstructive cases whereas in patients with obstruction uniform thickening of the entire left ventricular free wall was found

including the posterobasal part.^{21, 22} Asymmetric hypertrophy of the ventricular septum was more pronounced in that group. In another study absence of asymmetric hypertrophy of the inter ventricular septum was considered indicative of non obstruction during life. In those cases where asymmetry of the interventricular septum was present obstruction or non obstruction may have existed.² Absence of asymmetric hypertrophy of the septum did not deny a diagnosis of hypertrophic cardiomyopathy²³ and dilatation of the ventricular cavities prior to death may occur.²

Histologic histochemical and ultrastructural changes are similar to those that have already been noted but the distribution of abnormal myocardial fibers is different in the two clinical groups. In hypertrophic cardiomyopathy with obstruction the abnormal myocardial fibers and fibrils are mostly confined to the asymmetrically hypertrophied interventricular septum. In cases without obstruction the fibers are distributed focally through left and or right ventricular walls including the septum.^{24, 25, 26} These differences of distribution have been considered to account for the differences in clinical manifestations. Caution of interpreting these findings was however sounded. Such caution was well placed because other morphologic studies have shown widespread involvement of left ventricular walls in cases of patients with obstruction.²⁷ Twelve children with clinical evidence of obstruction have recently been described who showed at postmortem the characteristic distribution of non obstruction.²⁷

These studies on the different distribution of abnormal fibers and fibrils in the obstructive and non obstructive groups have shown that morphologic criteria are not altogether reliable in relation to clinical findings. The cases so far reported are relatively few and therefore further work must be undertaken to evaluate more fully these differences.

It may finally be concluded that despite the various observations and sometimes contradictory interpretations of the morphologic findings at macroscopic, microscopic and ultrastructural level one clear pattern has emerged. When sufficient material is available suitable for histologic histochemical and ultrastructural examination the combination of these methods permits diagnosis with a high degree of accuracy. Examination at necropsy of macroscopic and histologic

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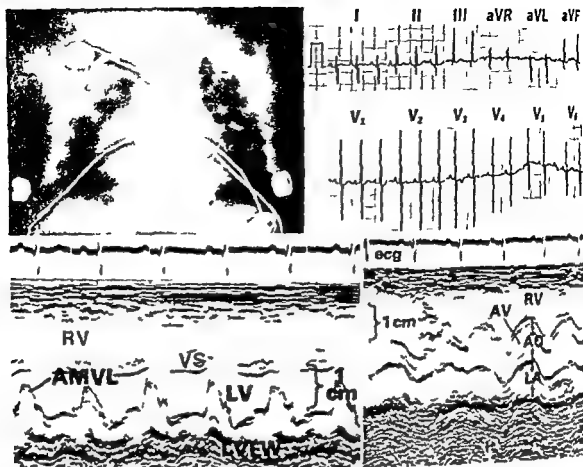


Fig 1 Posteroanterior chest radiograph (upper left) 2.5 months before death showing considerable prominence of the right sided chambers. The pulmonary vascular markings are prominent. Electrocardiogram (ECG) (upper right) obtained 3 months before death shows sinus tachycardia and biventricular hypertrophy. The echocardiogram (lower) obtained 1 month before death shows the right ventricle (RV), left ventricle (LV) and left atrium (LA) to be of normal size. The aorta (Ao) is at the upper limit of normal. The ventricular septum (VS) was normal. AVL = anterior mitral valve leaflet. AV = aortic valve.

cardiomegaly and evidences of increased pulmonary blood flow. The electrocardiogram (Fig 1) disclosed biventricular hypertrophy and the echocardiogram (Fig 1) disclosed no abnormalities. Despite furosemide, digoxin and supplemental oxygen, the congestive heart failure worsened. The feeding problem was found to be the result of partial antral obstruction. She died quietly.

At autopsy (A79 83) the heart weighed 34 gms (expected weight for her age = 29 gms). The right atrium was clearly dilated, the walls of the right atrium, right ventricle and left ventricle were thickened. The left atrium was normal in size. The four cardiac valves were normal. A large ventricular septal defect (VSD) located posterior and inferior to the crista supraventricularis, a large ostium secundum type atrial septal defect (ASD) and a patent ductus arteriosus (PDA) were present (Fig 2).

DR ROBERTS: The child presented had several

abnormalities associated with trisomy 13. Cabin will you describe the usual findings in patients with trisomy 13 and contrast them with those in patients with trisomy 18 and 21? DR CABIN: The abnormalities frequently found in patients with trisomy 13 are listed in Table 1, along with an indication of which abnormalities also are seen in trisomy 18 and 21. Our patient had several of the listed abnormalities (those with asterisks) and consequently the diagnosis of trisomy 13 in her was obvious and also confirmed by chromosome study. Diagnostic features of trisomy 18 include small lower jaw, palpebral fissures, clenched hand, short ear, narrow pelvis, short stature, and mental deficiency. Characteristic findings in infants with trisomy 21 include flat faces, protruding tongue, epicanthic folds, palpebral fissures, hypotonia, short hands, and mental deficiency. In all three trisomies and congenital heart disease is common.

Clinical pathologic conference

Congenital heart disease with trisomy 13

Use of the echocardiogram in delineating the location of a left-to-right shunt

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— William C Roberts MD
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DR ROBERTS Herein we will discuss a child with congenital heart disease and trisomy 13. Dr Cabin will present the patient's clinical and morphologic findings.

DR CABIN J M (CC No 13 31 03) was a 45 month old girl who died on July 10 1979. She weighed 24 kilograms at birth after a 37 week gestation. A precordial murmur was noted during the first 2 weeks of life and she was acyanotic. At age 15 days she was transferred to the Clinical Center of the National Institutes of Health because of feeding difficulties and intermittent signs of congestive heart failure. Her blood pressure was 70/40 mm Hg her heart rate was 172 beats/minute and the respiratory rate was 80 breaths/minute. Her head was small (microcephaly) both eyes were small (microphthalmia) and a fissure was present in the left iris (coloboma). She had a cleft upper lip and palate a preauricular skin tag transpalmar (Simian) creases partial fusion (frog like) of her toes (syndactylism) and a rudimentary extra digit (polydactyly) on her left hand and left foot. The right ventricular impulse was palpable. S was single and loud and a Grade 3/6 systolic ejection type murmur was heard along the upper sternal border. The lungs were clear. The chest radiograph (Fig 1) disclosed

Table 1 Major clinical and necropsy findings in trisomy 13 and the presence or absence of these findings in trisomy 18 and 21

| | Trisomy 13 | Trisomy 18 | Trisomy 21 |
|------------------------------|------------|------------|------------|
| Incidence | 1/5 000 | 1/4 000 | 1/700 |
| Increased maternal age | + | + | + |
| Survival beyond 1 year | Rare | Rare | Rare |
| Male:Female | 1:1 | 1:4 | 1:1 |
| Mental retardation | + | + | + |
| Feeding difficulty | + | + | ± |
| Deafness | + | + | 0 |
| Congenital heart disease | + | + | + |
| Microcephaly | + | 0 | 0 |
| Microphthalmia | + | 0 | ± |
| Cleft lip and palate | + | 0 | 0 |
| Malformed ears | + | + | + |
| Coloboms of the iris | + | 0 | 0 |
| Simian crease | + | + | + |
| Polydactyly | + | 0 | 0 |
| Syndactyly | + | + | 0 |
| Rocker bottom feet | + | + | 0 |
| Long hyperconvex fingernails | + | + | + |
| Undescended testes | + | + | + |
| Double renal pelvis | + | 0 | 0 |
| Abnormal olfactory bulbs | + | ± | 0 |
| Bicorpate uterus | + | 0 | 0 |

Indicates that this abnormality was present in our patient

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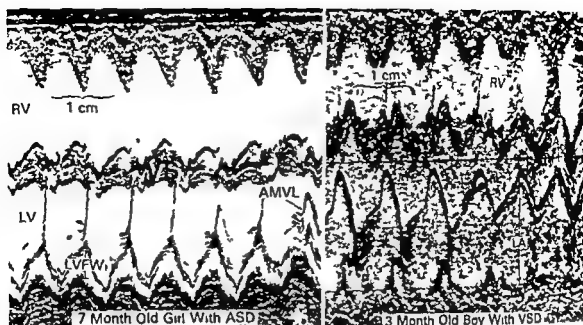


Fig 3 Echocardiograms from two patients. Left: A 7-month-old girl with a secundum type atrial septal defect (ASD). The right ventricle (RV) is dilated and the ventricular septum (VS) moves paradoxically during ventricular systole. The left ventricle (LV) is of normal size. LVFW = left ventricular free wall. AMVL = anterior mitral valve leaflet. Right: Echocardiogram from a 3-month-old boy with a ventricular septal defect (VSD). The left atrium (LA) is dilated and the aorta (Ao) is of normal size; consequently the LA to Ao ratio is increased.

cally. The aorta was mildly enlarged and the left atrial to aortic ratio was normal (1.0 [normal range = 0.8 to 1.2]). These findings are of considerable help in sorting out the level of a left to right shunt. Both VSD and PDA result in dilated left atria and left ventricles,^{2,3} because of volume overload of the left-sided chambers from the left to right shunt. The right ventricle may enlarge to some extent; the right atrium does not dilate. An ASD causes right atrial and right ventricular volume overload without left-sided enlargement. This right-sided overload may result in paradoxical movement of the ventricular septum during ventricular systole.^{4,5} Thus M-mode echocardiograms in infants with VSD (Fig 3) or PDA show increased left ventricular and left atrial dimensions with increased left atrial to aortic root ratios. ASD produces an increased right ventricular dimension; the left ventricular and left atrial dimensions are normal or smaller than normal and the left atrial to aortic root ratios are normal (Fig 3).

In our infant, all three chambers seen by the M-mode echocardiogram were normal in size and therefore the presence of ASD, VSD, or PDA as an isolated defect was most unlikely. The combination, however, of an ASD with a PDA and/or a VSD could result in a normal-sized left atrium, particularly if the atrial shunt were large.

The left or right ventricle could be normal or increased in size depending upon the relative magnitude of each shunt. Thus the M-mode echocardiogram in combination with the clinical findings in our patient suggested the diagnosis of ASD in combination with VSD and/or PDA.

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Fig 2 Longitudinal section of the heart. The walls of both the right (RV) and left (LV) ventricles are hypertrophied; a defect (D) is present in the most cephalad portion of the ventricular septum (VS); the right atrium (RA) is large and the aorta (Ao) and left atrium (LA) are of normal size. (Photo by M M M Moore.)

patients reported by Warkany and associates: congenital heart disease occurred in 27 (84%) of 32 necropsy patients with trisomy 13; in 83 (99%) of 84 patients with trisomy 18; and in 141 (52%) of 272 patients with trisomy 21. The most commonly found malformations in trisomy 13 were VSD, PDA, and ASD, and two or three of these three defects occurred more frequently than a single defect. These three defects also were common in patients with trisomy 18 and 21. The most common type of atrial septal defect in trisomy 21 is one located in the lowermost portion of the atrial septum (ostium primum or endocardial cushion type) and in trisomy 13 and 18 the defect most commonly is in the mid portion of the atrial septum (secundum type).

The occurrence in our patient of signs of congestive heart failure, acyanosis, and enlarged right-sided cardiac chambers with evidences of increased pulmonary blood flow strongly sug-

gested the presence of a left to right shunt at the atrial ventricular or great artery level or combinations of these three. The presence of trisomy 13 strongly suggested the presence of two or more of these defects.

DR ROBERTS: The echocardiogram has proved useful in delineating the level of a left to right shunt. Dr Lester has recently analyzed the usefulness of echocardiography for characterization and quantitation of a left to right shunt in patients with ventricular septal defect.² Dr Lester, can you summarize the echocardiographic findings in patient J M and from your previously collected data, how useful is the echocardiogram in predicting the level of the shunt in patients with left to right shunts?

DR LESTER: An echocardiogram was performed at 15 days of life (Fig 1). The left and right ventricles and left atrium were normal in size. The ventricular septum did not move paradoxically.

disease causes a granular cobblestone appearance with nodular filling defects corresponding to the exudative plaques seen endoscopically. The most common viral cause of esophagitis is herpes simplex, which tends to cause focal ulcers but may produce filling defects similar to moderate monilial disease.

Further investigation of the symptom of heart burn is indicated if the patient does not respond to therapy if there is a complication of the peptic esophagitis (such as stricture or ulceration) or if the diagnosis of esophagitis or gastroesophageal reflux is still in doubt. Esophageal manometry demonstrates a reduced lower esophageal sphincter pressure in 80 to 100% of patients with severe reflux esophagitis.¹⁰ A normal lower esophageal sphincter pressure suggests that reflux esophagitis is not the etiology of the patient's pain. In situations of continued suspicion of peptic esophagitis but equivocal manometric findings, direct demonstration of acid reflux is helpful.¹¹ Acid reflux may be demonstrated by placing a pH probe in the distal esophagus and instilling 0.1 N hydrochloric acid into the stomach. A fall in esophageal pH below 4 suggests the presence of reflux. This test has a greater than 90% yield in patients with reflux and very few false positive or false negative responses. A more recent method to demonstrate reflux is the use of a radioisotopic marker ingested with an exogenous fluid load.¹² Reflux of the isotope detected by gamma camera is an accurate and sensitive method but is not yet widely available.

If studies have demonstrated gastroesophageal reflux but there remains a question whether the patient has esophagitis, three other tests may be performed: the Bernstein Test, esophagoscopy and esophageal biopsy.¹ The Bernstein Test is a provocative test which reproduces the classic pain of reflux esophagitis by perfusion of the esophagus with 0.1 N hydrochloric acid. The acid is perfused in a blinded fashion alternating with saline. Saline will relieve the discomfort by washing acid from the esophagus. False positive responses are unusual and about 90% of patients have a positive response.

Esophagoscopy is helpful when it is not clear whether the patient's reflux is complicated by peptic esophagitis or when there is a complication of the peptic esophagitis such as stricture or ulceration which requires biopsy to exclude malignancy. Esophagoscopy permits biopsy or cytologic examination to detect other causes of esoph-

agitis, such as fungal or viral. However, the bits of tissue obtained through the flexible endoscope are often not adequate for histologic identification of reflux esophagitis. Visual assessment via the esophagoscope may be false negative or positive when the changes are subtle. Biopsy of the distal esophagus by a small capsule under fluoroscopic guidance provides accurate histologic identification of esophagitis. Less than 10% of normal controls will have evidence of esophagitis on such a biopsy, whereas approximately 90% of patients will have typical features.

Odynophagia or pain on swallowing is a second common cause of chest pain caused by esophageal disease. Depending upon the underlying etiology of the odynophagia, this symptom may be precipitated by swallowing solids or liquids. When the pain is the result of a mechanical disorder of the esophagus, both solids and liquids, especially if very hot or very cold, may cause symptoms. With obstructive lesions of the esophagus such as carcinoma or stricture, odynophagia is brought on more commonly by swallowing solid food. Irritant liquids such as fruit juice, coffee or spicy drinks may cause odynophagia if there is esophagitis.¹³ A barium swallow is the most important test to perform in a patient with odynophagia. This test will usually demonstrate structural abnormalities such as carcinoma or strictures and occasionally the mucosal irregularities of esophagitis or moniliasis or a motility disorder. Although chest pain is a major complaint in only 25% of patients with achalasia, a barium swallow will be abnormal in all. The characteristic findings are smooth tapering of the distal esophagus and nonperistaltic tertiary contractions. Diffuse esophageal spasm, however, may not show abnormalities on conventional barium swallow in spite of chest pain.

Cine radiography improves the diagnostic accuracy of the barium study when a motility disorder is present. Abnormalities in mucosal production of odynophagia will be recognized with a variable success on barium swallow.¹ If the study is of good quality, especially with air contrast, ulcerating carcinomas will be easily detected. The probability, however, of missing an early carcinoma of the esophagus as well as difficulty in detecting peptic or infectious esophagitis make esophagoscopy an important diagnostic tool in the evaluation of odynophagia.

If the barium swallow suggests a motility dis-

The digestive tract as a cause of chest pain

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Disease of the digestive tract may cause chest pain and be the chief complaint in a patient presenting to a cardiologist. A relationship of symptoms to the digestive functions of eating or defecation suggests gastrointestinal etiology. The autonomic nerve supply of the esophagus is similar to that of the heart, and pain from this organ often closely mimics cardiac pain. Of patients referred for gastrointestinal investigation because of angina-like pain but no other evidence of coronary artery disease, about half are found to have an esophageal etiology for the pain. Disorders of the stomach, duodenum, and biliary tree, and less commonly colonic, pancreatic, hepatic, or peritoneal disease can cause upper abdominal or chest pain. The problem may be either a functional motility disorder or a structural pathologic entity. The diagnostic problem is compounded when digestive disease and cardiac disease coexist. Occasionally provocative tests designed to elicit pain from the digestive tract give assistance, but frequently one must rely upon a clinical distinction.

Chest pain of esophageal origin

The three major types of chest pain of esophageal origin are heartburn, odynophagia (pain on swallowing), and spontaneous esophageal spasm. Heartburn is characterized by retrosternal burning sensation which travels up from the xiphoid and is made worse by certain foods and by recumbency.¹ In about 40% of patients pain radiates to the back, and in 5% it radiates to the arms or neck.¹ Heartburn is seen in increased frequency

in patients with scleroderma following resection of the lower esophageal sphincter during pregnancy and during medication with certain drugs especially anticholinergics. When heartburn is severe enough to be a major complaint, the patient should have a barium swallow which will reveal the major complications of gastroesophageal reflux: stricture and peptic ulcer of the esophagus. Barium swallow demonstrates gastroesophageal reflux in 10 to 25% of patients.² The finding of reflux may be increased to about 50% by the use of cine esophagography. The water siphon test (in which a water swallow relaxes the lower esophageal sphincter) or an acid barium swallow are designed to demonstrate reflux more frequently or initiate disordered esophageal motility if esophagitis is present; however, both of these tests have a high false positive response which limits their usefulness.³ The presence of hiatal hernia on barium swallow has been found to correlate poorly with gastroesophageal reflux and is therefore not a significant aid to the clinician.^{4,5} Functional integrity of the lower esophageal sphincter which prevents reflux of acid from the stomach into the esophagus and esophageal peristalsis which clears acid from the esophagus are the significant determinants of peptic esophagitis.

Studies of the esophagus by barium swallow deserve special mention not only because they are the first studies needed in evaluating suspected esophageal disease but also because of recent improvements in technique.⁶ The most notable improvement in technique is the use of air contrast. The earliest manifestations of esophagitis recognized with confidence are superficial erosions or ulcers. Occasionally edema of the subtle transverse esophageal folds is noted. Local areas of eccentric decreased distensibility or finely nodular mucosa are chronic changes. Monilial esophagitis, the most common infectious esophageal

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this therapy as would be expected or if there are atypical features which suggest esophagitis of other etiologies then esophagoscopy often with biopsy or cytologic brushings is indicated. If the barium swallow and esophageal manometry are typical of diffuse esophageal spasm and the Bernstein Test does not reproduce the patient's pain the patient may be treated with anticholinergics or nitrates without further investigation.

Other organic disease

Although structural disease of the remainder of the gastrointestinal tract, biliary tree, pancreas, liver, or peritoneal cavity may produce pain in the upper abdomen or lower chest, these disorders often have features which distinguish them clinically from cardiac pain and they may be readily diagnosed if they are considered. Ulcers within the stomach or duodenum occasionally cause lower chest pain, but the typical burning pain with relief following meals or antacids mandates the performance of an upper gastrointestinal x-ray. Occasionally a patient will have a superficial ulcer or gastritis in a normal stomach or an ulcer in an area difficult to evaluate radiographically (for instance, an ulcer in a patient with a Billroth II operation) and endoscopy reveals the pathology. Biliary colic may cause pain in the high epigastrium and occurs within a few hours following a meal but may also be spontaneous. Biliary colic is a misnomer since the pain is usually constant and lasts for one half hour to several hours. The pain is often associated with nausea and vomiting and may radiate into the right scapula or right upper quadrant. Acute cholecystitis may also cause high epigastric discomfort but is more likely to be associated with right upper quadrant pain and tenderness. This pain is of longer duration than the pain of biliary colic and is associated with signs of inflammation such as leukocytosis or fever. An oral cholecystogram or ultrasound of the gallbladder are reliable tests in over 95% of patients for the detection of gallstones. Ultrasound is especially useful in the jaundiced patient. Acute cholecystitis may be ruled out by gallbladder visualization on oral cholecystogram or gamma camera scanning following injection of one of the newer radionuclides excreted in the bile.

Acute pancreatitis pain radiates through into the back, is persistent, and usually is associated with an elevated serum amylase or urinary amyl-

lase clearance. The pain of chronic pancreatitis is also persistent and penetrating to the back, the epigastric area, with exacerbation following meals or drinking of alcohol. Pseudocysts of the pancreas are notorious for their ability to protrude in unusual locations. Dissection of a pseudocyst into the mediastinum may cause chest pain and dysphagia. Chronic pseudocysts have been reported to have normal serum amylase in up to 50% of patients. Occasionally pseudocysts may erode into the pleural space causing a pancreaticopleural fistula and generate chronic chest pain. A chest x-ray will show a pleural effusion especially on the left. Endoscopic retrograde pancreatography is of value in diagnosing chronic pancreatic disease (small cysts, chronic pancreatitis, fistula, or carcinoma) and in assisting the surgeon in planning appropriate operative intervention. Abdominal ultrasound or computerized tomography are other valuable noninvasive tests which detect pancreatic, hepatic, or subphrenic disease.¹

Functional gastrointestinal disorders causing chest pain

Motility disorders of the intestinal tract and biliary tree are more difficult to identify than the structural disorders mentioned above. Irritable bowel syndrome is now widely accepted as a distinct disorder which can be identified by specialized motility studies. Recent investigations have revealed that muscles of the large intestine in these patients have an abnormal myoelectric activity in the resting state with a predominance of three cycle per minute activity in contrast to the normal predominance of six cycles per minute.²¹ These patients also show abnormal postprandial colonic spike potentials and contractions.²² Normal individuals respond to a meal containing fat by rapid increase in colonic contractions which subside over an hour and a half. Patients with irritable intestine on the other hand demonstrate a delayed increase in motility activity which peaks at a time when the normal activity is decreasing. Colonic motility studies are performed only in a few centers and under these circumstances we must rely upon exclusion of structural disease and typical symptoms.²³ Patients with irritable intestine characteristics are young adults with a chronic history of recurrent abdominal pain exacerbated by meals. They may experience diarrhea or constipation or both.

Table 1 Diagnostic procedures to evaluate gastrointestinal causes of pain

| Organ | Suspected disorder | Primary tests | Secondary tests |
|-----------------------|--------------------------|--|-------------------------------------|
| Esophagus | Esophagitis | Barium swallow Esophageal manometry Esophagoscopy and biopsy Bernstein Test | pH probe Reflux scan |
| | Obstructive lesion | Barium swallow Esophagoscopy and biopsy | |
| | Motor disorder | Barium swallow Esophageal manometry Esophagoscopy | Cine-esophagogram Bernstein Test |
| Stomach and intestine | Ulcer | Upper gastrointestinal series, duodenoscopy | |
| | Irritable bowel | Barium enema Proctoscopy | Colonic motility studies |
| Biliary tree | Gallstones | Oral cholecystogram Abdominal ultrasound | IV cholangiogram Biliary scan |
| | Dyskinesia | ERCP ? Sphincter of Oddi manometry | ? Morphine test |
| Pancreas | Acute or chronic disease | Serum amylase Abdominal echo or CAT ERCP | |

lower esophagus esophageal manometry will give significant clinical information. In achalasia peristalsis is absent and may be replaced by nonperistaltic (tertiary) waves. The pressure of the lower esophageal sphincter is elevated and undergoes incomplete relaxation on swallowing. In diffuse esophageal spasm there are tertiary contractions of the esophagus but some peristaltic activity is preserved. The tone of the lower esophageal sphincter may be normal or in some cases elevated and may simulate that seen in achalasia.² Swallows of hot or cold liquids may precipitate tertiary contractions in these patients. Esophagoscopy is indicated in patients with achalasia not only because of the long term risk of carcinoma superimposed upon achalasia but because of the ability of carcinoma of the distal esophagus or adjacent structures which has invaded the esophageal nerves to mimic achalasia. Patients in whom carcinoma is producing a radiographic and manometric picture identical to achalasia tend to be older to have symptoms for several months only and to have weight loss in excess of that expected from the duration of their esophageal symptoms.

The third type of chest pain of esophageal origin is spontaneous chest pain caused by diffuse esophageal spasm. The pain of spontaneous diffuse esophageal spasm is similar to the crushing substernal chest pain induced by eating in

patients with odynophagia.³ Spontaneous esophageal chest pain is usually caused by an esophageal motor disorder. It occasionally is a manifestation of carcinoma or esophagitis. When the spontaneous esophageal spasms are the result of esophagitis appropriate therapy of the esophagitis may relieve the spasm and pain. Patients whose esophageal spasm is a manifestation of a primary motor disorder may obtain relief by the use of nitroglycerin. Symptomatic relief of esophageal pain by sublingual nitroglycerin simulates the response seen in cardiac pain. Esophageal discomfort however is not brought on by exertion or relieved by rest. Often the patients with spontaneous esophageal chest pain and spasm will have odynophagia or dysphagia. The initial diagnostic test is a barium swallow as in the case of patients with heartburn or odynophagia. Because these patients are most likely to have a motor disorder especially diffuse esophageal spasm esophageal manometry is usually the next procedure performed. At the time of esophageal manometry it is often valuable to perform a Bernstein Test to reproduce the patient's symptoms if they are secondary to esophagitis. If the barium swallow shows reflux from the stomach the Bernstein Test is positive and the lower esophageal sphincter pressure is reduced it is reasonable to treat such patients with antacids or cimetidine.³ If the patient does not respond

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notice mucus on the bowel movement. Most patients have lower abdominal crampy pain but patients with the so called splenic flexure syndrome have left upper quadrant pain which may radiate to the shoulder. In order to establish a diagnosis of irritable intestine one must first exclude other diseases with a normal upper intestinal x-ray and barium enema. In addition most clinicians insist upon a normal proctoscopic examination and no evidence of inflammation on white blood count or erythrocyte sedimentation rate. The pain and bowel irregularities of these patients may respond to low fat high fiber diet and to anticholinergic therapy.

Biliary dyskinesia is a poorly documented phenomenon for which there is beginning to emerge objective evidence. The pain of these patients mimics biliary colic but gallstones or structural abnormality are not found. If the gallbladder is present it empties poorly in response to intravenous cholecystokinin infusion or fatty meal and the characteristic pain is reproduced. Some investigators have noted the gallbladder to distend as if straining to empty against a resistance. There is controversy regarding the significance of these findings and surgical therapy must be undertaken with great caution. Poor gallbladder emptying is also seen in diabetic and post vagotomy patients but does not cause symptoms.

Another group of patients with suspected biliary dyskinesia are those who have previously undergone a cholecystectomy but present with similar biliary symptoms. Good visualization of the bile duct is essential to document the absence of organic disease. Intravenous cholangiography has a high false negative rate and retrograde transhepatic or operative cholangiography is needed. Recent and as yet unconfirmed evidence suggests that these patients have an elevated sphincter of Oddi pressure determined during endoscopic retrograde cannulation. The bile duct may be slightly dilated and the radiographic dye may drain slowly. Others have advocated the use of a morphine and cholinergic stimulation test which reproduces the patient's pain and causes elevated serum amylase lipase or liver enzymes. The value of this provocative test has been questioned by findings that normal volunteers may also have an increase in these enzymes or experience pain following morphine and cholinergic stimulation. Although it remains difficult

to obtain objective evidence of post cholecystectomy biliary dyskinesia some centers have reported beneficial effects of sphincteroplasty especially when the septum between the bile duct and pancreatic duct is divided. Long follow up of patients chosen for sphincteroplasty because of abnormal sphincter pressure is not yet available. Sphincteroplasty is difficult has significant morbidity and must be undertaken only following the most careful clinical assessment. When surgery is performed on the bile duct the surgeon may describe a thickened septum between a common bile duct and the pancreatic duct. Medical therapies which have been tried in these patients include anticholinergics long acting nitrates and low fat diets. As is the case with gallstone patients most of the patients are female and they often have had symptoms for a prolonged period prior to cholecystectomy.

In summary various gastrointestinal disorders may cause chest pain. In most cases a distinction between these disorders and cardiac disease can be made by history. The most difficult condition to distinguish from cardiac disease is symptomatic diffuse esophageal spasm but history, barium swallow and especially esophageal manometry have now allowed an easier distinction to be made.

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reach or decrease below the 95th percentile of the age group of the patient we proceed with drug treatment. Our mean values for plasma cholesterol levels and the 95th percentile cutting points are given in Table I. Our 95th percentile for plasma triglycerides is 200 mg %.

The drugs presently available on the market are few in number, have limited efficacy, and may have multiple side effects. Instead of being complete or exhaustive I shall restrict myself to the description of those drugs that are the most effective or the most widely used for the treatment of hyperlipidemia.

Clofibrate (CPIB) Ethyl p chlorophenoxyisobutyrate (CPIB) is a branched chain fatty acid ester.

Indications Clofibrate is the drug of choice in the treatment of hypertriglyceridemia. Many patients with combined hyperlipidemia also respond.

Effect Clofibrate reduces plasma triglyceride levels by about 30% to 40% and plasma cholesterol levels by 5% to 15%. In hypertriglyceridemic patients LDL and HDL concentrations increase and VLDL decreases. The response in hypercholesterolemia is poor.

Mechanism of action Sterol balance measurements indicated a significant increase of the fecal excretion of cholesterol end products (neutral sterols)² and a decrease of cholesterol absorption⁴ during clofibrate administration inducing a negative sterol balance (more cholesterol end products coming out than cholesterol going in). The action on triglycerides seems to be both a decrease of VLDL production and acceleration of its catabolism to LDL. Or simply endogenous triglycerides are synthesized slower by the liver and once made they are broken down faster.

Side effects Nausea and diarrhea may rarely occur. We have seen a few cases of myalgia with elevated CPK levels returning to normal after cessation of drug administration. It has been shown that the drug produces lithogenic bile and both the CDI⁵ and the WHO study⁶ demonstrated increased rates of cholelithiasis and diseases of the biliary tract in patients receiving clofibrate.

Drug interactions Clofibrate increases the effect of coumarin anticoagulants. Patients should be carefully monitored on both medications.

Dose and costs Dose is 500 mg capsules four

times daily (or two capsules twice a day). In January 1980 the cost to our pharmacy was \$48.18 per 100 capsules.

Cholestyramine and colestipol are unabsorbable high molecular weight anion exchange resins.

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Effect These compounds reduce plasma cholesterol levels by about 20% to 30%. Plasma triglycerides may moderately increase during administration. LDL cholesterol is decreased. VLDL triglycerides may moderately increase and HDL remains unchanged.^{1,7}

Mechanism of action Cholestyramine and colestipol bind bile acids in the gastrointestinal tract, thereby interrupting the enterohepatic circulation. Bile acids are an important end product of cholesterol metabolism and their increased fecal excretion leads to a more rapid conversion of cholesterol to bile acids which significantly decreases the plasma cholesterol concentration. Cholesterol absorption is somewhat decreased but only if the drug is taken before meals.¹

Side effects Constipation is the most frequently seen complication, sometimes improved by the use of stool softeners. The taste and consistency of the resins which are not soluble in water may also be unpleasant.

Drug interactions It may reduce the absorption of a number of compounds (digitalis, bismuth, soluble vitamins, iron, thyroid preparations, tetracycline, thiazides, etc.). It is recommended that any other medication be taken at least 1 hour before the resins.

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Nicotinic acid This is a vitamin of the B group (niacin) which prevents pellagra, given in much larger doses to reduce plasma lipids.

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Effect Nicotinic acid lowers plasma cholesterol

Appraisal and reappraisal of cardiac therapy

edited by Arthur C. DeGraff and Julian Frieden

Drug treatment of hyperlipidemia

Paul Samuel, M.D.

New York, N.Y.

During the past decade we have witnessed one of the major controversies of modern pharmacology in the field of drugs used for the treatment of hyperlipidemia. First as is frequently the case, the lapse of time improved methodology and the advent of large clinical trials have demonstrated significant and hitherto unsuspected side effects of a number of drugs widely used in the field. Clofibrate was shown to induce gallstone formation^{1,2} and thyroxine caused significant cardiac arrhythmias³; estrogens increased thromboembolic complications⁴; just to mention a few. Second, the validity of drug intervention itself has become the subject of controversy and has been seriously questioned. The results of the Coronary Drug Project and of the World Health Organization trial⁵ showing no difference in cardiovascular mortality rate between patients in the control and drug treatment groups have raised concerns about the validity and efficacy of drug treatment in this field.

Justifiably the question has to be asked: what are we treating: numbers or people?

And yet despite the controversy we are faced with more and more evidence which indicates that increased plasma lipid levels are a significant health hazard and ought to be reduced by whatever means. The epidemiologic evidence is overwhelming indicating increased risk of cardiovascular disease as plasma lipids go up. Concerning the clinical trials, the reduction of plasma cholesterol levels in the CDP⁶ was only 6% with clof-

Table 1 Average plasma cholesterol concentrations and 95th percentiles according to age

| Age (years) | Mean plasma cholesterol | 95th percentile (mg/dl) |
|-------------|-------------------------|-------------------------|
| 12-17 | 166 | 228 |
| 21-29 | 193 | 260 |
| 30-39 | 212 | 270 |
| 40-49 | 228 | 280 |
| 50-59 | 230 | 290 |

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Center for the Prevention of Premature Atherosclerosis, Rockefeller University

brate. One would really not expect too much of that. Conversely in the WHO study⁵ there was a significant reduction in the incidence of nonfatal myocardial infarction yet this result was obtained with only a 9% reduction of serum cholesterol levels. (Similar results were seen with nicotinic acid in the CDP⁶). Moreover in the WHO study the reduction of myocardial infarction in the clofibrate treated group was most marked in men who experienced the largest reductions in plasma cholesterol levels. Thus the results of the WHO study offer the first clear cut support for the lipid hypothesis⁷ which postulates that reducing plasma cholesterol by whatever means should lead to a lower incidence of cardiovascular morbidity and mortality.

Whom to treat?

The primary treatment of hyperlipidemia is dietary. The preceding article describes its modalities in detail. But who should be treated with drugs and with what drugs? At the outpatient clinic of The Rockefeller University Hospital our guideline is to initially institute dietary treatment for not less than three months. If at the end of that period plasma lipid levels have failed to

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reach or decrease below the 95th percentile of the age group of the patient we proceed with drug treatment. Our mean values for plasma cholesterol levels and the 95th percentile cutting points are given in Table I. Our 95th percentile for plasma triglycerides is 200 mg %.

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Effect Nicotinic acid lowers plasma cholesterol

October 1980 Vol 11

Table II Effect of clofibrate, neomycin and colestipol therapy on body masses of cholesterol

| Study | n | Ma (gm) | M (gm) | M/Ma (gm) |
|-------------------------|----|---------|---------|-----------|
| Control | 11 | 38 | 109 | 71 |
| Clofibrate | | 28 | 77 | 49 |
| Difference (%) (Ref 5) | | 10 (26) | 32 (39) | 22 (31) |
| Control | 4 | 36 | 103 | 67 |
| Neomycin | | 22 | 61 | 48 |
| Difference (%) (Ref 16) | | 14 (39) | 33 (37) | 19 (28) |
| Control | 7 | 21 | 50 | 31 |
| Colestipol | | 23 | 55 | 32 |
| Difference (%) (Ref 17) | | — | — | — |

Ma = Rapidly exchangeable pool of cholesterol (Plasma + RBC + liver + gut)

M = Minimum estimate of total body mass of cholesterol (except CNS)

1M = Slowly turning over masses of tissue cholesterol

levels by about 8% to 16% and triglycerides by 1% to 30%. It lowers plasma free fatty acids, LDL and LDL and it increases HDL levels.

Mechanism of action It is frequently stated to be unknown. Nicotinic acid was shown to decrease lipolysis, decrease the hepatic production of triglycerides and increase fecal excretion of cholesterol end products (neutral sterols).

Side effects are unfortunately numerous and patient acceptance is poor. It seems to me that for this reason the drug is only a second line compound. The main problem is intense cutaneous flushing and pruritus. Starting with small doses (100 mg in the middle of meals) and increasing the dose gradually may somewhat alleviate this symptom. Anorexia, nausea, vomiting, diarrhea and activation of peptic ulcer have been reported. Glucose intolerance, impaired liver function tests and hyperuricemia may also occur.

Drug interactions May potentiate the effect of osmotic laxatives or hyperuricemic diuretics.

Dose and costs Begun with 100 mg tablets three times daily and increase gradually to one gram (two 500 mg tablets) in the middle of three meals (3 gm per day). In January 1980 the cost of our pharmacy was \$1.50 per 100 (500 mg) tablets.

Neomycin Neomycin is a broad spectrum aminoglycoside antibiotic poorly absorbed from the gastrointestinal tract (< 3%). It lowers plasma cholesterol levels at very low doses of administration (0.5 to 2 gm daily).

Indications Hypercholesterolemia.

Effect The drug reduces plasma cholesterol

levels by 20% to 30% sometimes even in patients with resistant familial hypercholesterolemia.

Mechanism of action Neomycin decreases cholesterol absorption and increases fecal cholesterol end product (neutral sterol) excretion leading to a negative sterol balance. Its effect may be mediated through its action on the intestinal bacterial flora (markedly decreased 7 α -dehydroxylase activity of intestinal bacteria) or by interfering with micelle formation in the lumen of the gastrointestinal tract.

Side effects One third to half of patients on neomycin have transitory diarrhea or abdominal cramps that usually subside after 1 or 2 weeks. Lomotil is helpful for this symptom. The small amounts of neomycin absorbed from the gut are excreted by the kidney; thus normal renal function is an absolute prerequisite for using the drug. Ototoxicity has been reported in very rare cases. We perform periodic hearing tests in patients treated with neomycin. At higher dose levels (12 gm daily) steatorrhea, renal damage, staphylococcus enterocolitis, moniliasis and multiresistant coliform overgrowth have been reported; however, we have not observed these complications with the small doses used for cholesterol reducing purposes.

Drug interactions Digoxin should be administered one hour before neomycin is given, inasmuch as there may be interference with its absorption. The possibility exists that coumarin anticoagulants may be potentiated by the drug.

Dose and costs Tablets of 0.5 gm of neomycin sulfate three or four times daily after meals (two

Coxsackieviruses and chronic valvular heart disease

Acute rheumatic carditis of streptococcal etiology is considered to be the predominant cause of chronic valvular heart disease (CVHD). Hence there is a tendency to assume that all or most cases of CVHD are of rheumatic origin. This has resulted in an inadequate search for other possible etiological factors in CVHD.

It is now clear that several infectious agents can cause endocarditis and valvulitis in man and animals. These agents are group B coxsackieviruses (CBV), adenovirus, encephalomyocarditis virus, virus B, inflammatory fibromyoma virus, vaccinia virus, pseudorabies virus, varicella virus, *Chlamydia psittaci*, *Coxsackie burnetti* and *Mycoplasma gallisepticum*. Among these CBV form an important group.

The relationship between viruses and CVHD may be investigated (1) in experimental animal models, (2) by following up the clinical course of individuals with viral myocarditis and (3) by investigating patients with CVHD.

Endocarditis and valvulitis are caused by CBV infection in mice and in cynomolgus monkeys. They also cause CVHD in cynomolgus monkeys with pathological changes similar to those of human rheumatic heart disease.

In human viral myocarditis the cardiac valves may be affected either directly as a result of valvulitis or indirectly by the involvement of the valve ring and the valve apparatus due to cardiac dilatation. It would be reasonable to assume that the more severe the myocarditis, the greater the likelihood of valvulitis and consequent CVHD. However, an evaluation of the published reports of the follow up of patients with viral myocarditis has been difficult because the data available are incomplete. Babb and colleagues reported on four patients ranging in age from 4 to 19 months with CBV myocarditis. A 13 month old child had no murmur on the phonocardiogram and only a slight cardiac enlargement seen on the chest x ray at the time of his acute illness. However this child had an apical systolic murmur without cardiac failure 4 months later. The second patient, a 4 month old infant, had a normal chest x ray and ECG but the phonocardiogram showed a mid-diastolic murmur. A systolic murmur of the ejection type during the acute illness five months later there was still a slight systolic murmur. The third patient was a 4 month old infant with a normal chest x ray and ECG but was in edema and had a blowing systolic murmur. This murmur disappeared by the twelfth day and the child was well thereafter. The fourth patient had no evidence of valvular disease.

Smith reported on 11 patients with CBV myocarditis four of whom had normal hearts and the other seven had enlarged hearts and abnormal ECG. The third had only an abnormal ECG. The fourth had a pansystolic murmur followed by a short mid-diastolic murmur presumed to be of viral infection. This

patient was later admitted for a proved viral myocarditis to CBV type 4. There is no mention of previous valvular damage during follow up. In a later report of 6 patients there were 3 with myocarditis and residual valvular disease with or without mitral incompetence. Clinical details during admission were incomplete.

Sainani and co-workers have reported on 2 patients with proved CBV myocarditis of whom eight had systolic murmurs including one with an apical mid-diastolic murmur. There was diffuse cardiac enlargement in 1 patient. Clinical and radiological correlations were given. Of the 11 followed up one had a systolic murmur for 30 months, another for 19 months and a third had a short mid-diastolic murmur for 6 months. In a later report of 19 patients with CBV myocarditis whom 13 had Grade 2/6 apical systolic murmurs at acute stage. None of them had murmurs during follow up.

Bengtsson studied 90 patients with cardiac involvement following infectious diseases, of whom 24 had a variety of infections. A systolic murmur was present in 10 patients had diastolic murmurs. The persistence of involvement is not mentioned in their report.

Gerzen et al. reported on the follow up of 40 patients with acute myocarditis, 7 of whom had a viral etiology. They had evidence of valvular involvement.

Thus the reports on patients with CBV myocarditis show that valvular involvement in the acute phase is frequent. However the follow up reports do not give a picture of the frequency of CVHD. Myocarditis due to viruses seems to be less often associated with valvular involvement.

Burch and colleagues, using immunofluorescence technique studied 50 routinely autopsied hearts. CBV were found in the myocardium in 30.5% and in the aortic valve in 5.4%. The prevalence was higher in children than in adults. Later Burch and Cooke have demonstrated CBV type 4 antigen in the areas of myocardial damage including the aortic valve in a patient with regurgitation myocarditis and nephritis.

Ward and Ward examined left atrial and aortic valve specimens from patients with CVHD by indirect immunofluorescence for the presence of antigens of a variety of viruses (polio types 1-3, influenza A, echo type 16, CBV, *Chlamydia psittaci* and *Mycoplasma pneumoniae*). CBV antigen was found in one or more cases. There was a positive for two or three unrelated antigens. There was a difference in the frequency of detection of the virus with and without a history of rheumatic fever.

Thus, the investigations on patients with CVHD give support to a possible virus etiology in valvular heart disease. Further evidence for CBV involvement in the

cessity of individual judgment in this field is evident

It is clear from the foregoing that in most patients we can lower plasma lipids by drugs which may have side effects. Thus the risk and benefits must be carefully weighed

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Cardiopulmonary resuscitation—an element of sophistication in the 18th century

Drowning or near drowning accidents appear to have been as prevalent in the 1700s as they are today. Interest in the aggressive treatment of drowning or near-drowning victims has always been great for these individuals were usually in good health and because it has become apparent that survival is possible even after as long as 40 minutes below the surface. Eighteenth century reports of survivals after hours under water have been noted but of course would be difficult or impossible to confirm. During the latter half of the 18th century however elements of the pathophysiology of drowning were recognized. Hosack discusses popular opinions by "distinguished writers" on the subject that in essence point to the primacy of hypoxemia— it is probable that the death which ensues or seems to ensue in drowned persons is entirely owing to the stopping of respiration and to the ceasing in consequence of the circulation of the blood. Laryngospasm was also recognized— a contraction of parts about the larynx preventing the air from passing into or out of the lungs. The lack of significant amount of water in the lungs of some individuals at autopsy was also known.

The interest in this in providing assistance to the drowning was limited to the establishment of societies in the 17th and 18th centuries first in Amsterdam then in London. These societies first in Amsterdam then in London were concerned with the procurement of books and manuscripts on the subject of drowning and kept in good order. Advice on related subjects was given and unacceptably slow progress was made in research and new apparatus were not granted monetary grants to the already existing knowledge. It was claimed by

Hosack that nearly one thousand persons were preserved from death in a 20 year period by the societies in London and London.

A clear concise approach to the management and treatment of the victims of drowning (near-drowning) was published by the Humane Society of the State of New York as well as by Hosack. These same therapeutic principles were reviewed about ten years later in a chapter of the book by Reece. Early attention to potential hypothermia was noted. The rapid reestablishment of respiration. Mouth to mouth or mouth to nose approaches to restore the lungs were suggested though a bellows was considered. Hosack favored inserting a tube into the trachea which tube a bellows was connected an approach not dissimilar to our present-day effort. He noted that this approach allowed air to be blown directly into the lungs whereas other methods were associated with passage into the stomach. He made note of one of rejection to the bellows namely that it had to be removed and reinserted. Though mouth to mouth or mouth to nose respiration was apparently used at that time he mastered the art "blown in from the lungs of another person" and therefore must render the blood flow and circulation thus before. Hosack reviewed clear tracheal intubation and claimed that one of it might be that it spared the patient bronchitis— as air may thereby be blown into the lungs as opposed to an opening into the wind pipe.

Lack of response to the above resuscitative effort was recognized as being related to cardiac arrest. Modern reviews of the subject of drowning point out potential cardiac arrhythmias and conduction disturbances could be related to the hypoxemia and have been

Table 1 Geometric mean titers of antibody to
 up B coxsackieviruses

| | Type | | | | | |
|----------------------------|------|----|----|----|----|----|
| | B1 | B2 | B3 | B4 | B5 | B6 |
| Unmatched control (n = 58) | 13 | 16 | 11 | 19 | 10 | 8 |
| HD with h/o RF (n = 12) | 14 | 26 | 11 | 49 | 10 | 14 |
| HD without h/o RF (n = 16) | 8 | 9 | 14 | 7 | 8 | 12 |

o RF = history of rheumatic fever CVHD = chronic valvular
 disease

HD was the subject of a recent preliminary report by us
 from 79 patients with mitral stenosis and from 58
 matched controls were examined for the prevalence and
 of neutralizing antibodies to CBV types 1-6. There
 is statistically highly significant differences between
 patients and controls in the titers of antibody to CBV type 3
 14 and in the prevalence of antibody to type 3. Among the
 patients 12 had a previous history of rheumatic fever and 16
 not. In one patient the history was equivocal. The
 geometric mean titers of antibodies in these patients are
 given in Table 1. Clearly, the mean titers of antibody to CBV
 types 3 and 4 were considerably higher in patients without a
 history of rheumatic fever than in those with such history.
 Some patients with CVHD do not have a history of
 rheumatic fever. While there has been a reported decline in
 prevalence of acute rheumatism and consequent CVHD,
 decline in the prevalence of CVHD without preceding
 rheumatic fever has been observed. This further supports the
 concept of nonrheumatic CVHD which is embodied in newer
 terms such as "rheumatic type" valvular deformity and
 virus valvular heart disease.

It is also possible that in some cases of CVHD the valve
 deformity may be the result of damage produced by sequential
 subclinical attacks of rheumatic and/or virus valvulitis.
 Perhaps such valvular deformity is more commonly stenotic
 rather than regurgitant for the following reasons. It is the
 patient with mild rheumatic carditis who is more likely to
 develop a stenotic valvular lesion. On the contrary those with
 regurgitant valvular deformities more often give a history of
 preceding severe rheumatic carditis. It is also known that
 patients with stenotic valvular lesions give a history of acute
 rheumatism less often than those with regurgitant valvular
 disease.

More intensive studies on a large number of patients with
 stenotic and regurgitant valve deformities and a follow up of
 those with proved viral myocarditis for evidence of preexistent
 valvular disease may result in a change of our present
 knowledge on the etiological factors responsible for chronic
 valvular heart disease.

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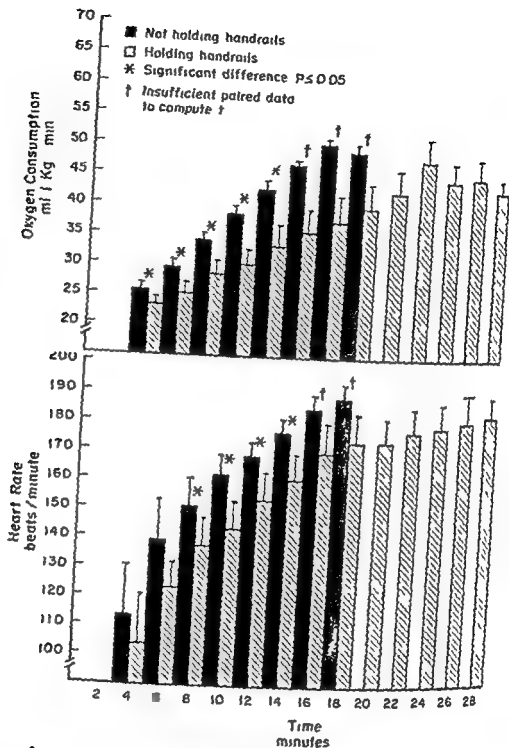


Fig. 1 Oxygen consumption and heart rate responses to experimental conditions

levels. A walking protocol of 1.1 m/s was used to minimize differences in mechanical efficiency.

Heart rate was monitored using standard electrocardiographic procedures while oxygen consumption was measured serially with a Beckman 8250 system. Calibration of the system was performed before and after each test. Attainment of maximum oxygen consumption by each volunteer was considered as established by Mitchell and colleagues when the criteria of 1.5 l/min/kg and 170 beats/min were met.

Data were treated with non-directional t -tests to determine whether differences existed ($p < 0.05$).

Fig. 1 illustrates the oxygen cost and heart rate response to each condition. The differences were statistically significant ($p \leq 0.05$). In all cases, observed values were lower when subjects were allowed handrail support. The oxygen consumption and heart rate values were not significantly different when both conditions were compared. Comparison of exercise duration under both conditions illustrated a dramatic increase when handrail support was permitted ($p \leq 0.01$). Mean values for oxygen consumption

sorders associated with that state. The concept of closed chest cardiac massage was not recognized in the 18th century. It is a need to do something for the cardiac situation no doubt to the recommendation for the use of electricity. Hosack refers that the rationale for the use of electricity was its then established and well recognized action on the muscle. It was in the 1780s that Galvani observed that by touching the nerves or the muscles with a piece of metal connected to an electrostatic machine, the muscles could be made to contract. The Humane Society of New York believed electricity to be a most powerful agent, a very proper remedy. The society warns however that in all cases the machine should be made to excite powerfully, otherwise the attempt to use it will be a loss of time, and so the precious moments of recovery may be lost forever. A procedure was outlined by which the patient was "electrified for four or five minutes, the hand of one of the attendants being applied close to the body so as to take strong sparks which should be drawn from the left side over the heart. If that procedure did not produce the appearance of life or motion, they recommended that light shocks (which should be increased each session) should be sent from the breast bone through to the neck or from side to side so as to excite the heart to action if possible. This latter effort would certainly appear to be in line with our present day concepts of closed chest cardiac resuscitation as demonstrated by Zoll. These early investigators did warn of the need for this procedure to be performed only by experienced operators. Hosack also warns that to get a electrical apparatus in readiness requires a considerable length of time, especially on a damp day, in which time the tent spark of life may be entirely destroyed. On reading the above one cannot help but wonder whether these patients on canon and quite fortuitously might have been helped by fibrillation (we are all aware of how small a shock is occasionally effective in cardioversion of various arrhythmias).

or periods of cardiac pacing (the repeated light shocks applied to the chest). Could the latter have been the forerunner of the external pacemaker, a concept which did not become a reality for another 150 years?

How many lives were actually saved by these methods would be impossible to estimate. One cannot help but be impressed by the degree of sophistication suggested by the practitioners of that period. Principles and therapeutic interventions common to the practice of cardiopulmonary resuscitation that most would have associated with modern medical practices, were actually in vogue almost 200 years ago.

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Errors in predicting functional capacity from treadmill exercise stress test

Exercise stress testing as a diagnostic procedure for ischemic heart disease has been used by qualified physicians for many years. Since physical activity has been shown to be a useful modality for improving functional capacity in cardiac patients, knowledge of the individual's aerobic level and heart rate response is essential if such prescribed activity is to be administered safely and effectively. Though direct oxygen consumption measurements are more accurate than predicted values, especially with cardiac patients, the additional equipment and procedural requirements make such an evaluation either practical nor economical in many clinical situations. As a result, nomograms, tables, and formulae have been developed for estimation of the patient's ability to use oxygen. Such estimates have been derived from exercise of a highly standardized nature. It has been suggested that wide variations

about estimated values can be expected, especially if protocols used for particular nomograms or tables are not strictly followed. Thorough documentation of these variations have not been reported. The purpose of this investigation was to compare oxygen consumption values during a progressive treadmill exercise stress test while either allowing subjects to use handrails for enhanced stability or not allowing such assistance.

Six healthy male volunteers who were classified as following an active lifestyle but who were not considered to be in a trained state were used as subjects. Their characteristics expressed as mean values were: age = 26.6 (± 2.1) years, weight = 71.5 (± 3.3) kilograms, percent body fat = 12 (± 2.3), and maximum oxygen consumption = 48.1 (± 5.9) ml/kg/minute. In each case, the subject worked to maximal

otocols were 15 ± 276 minutes and 95.2 ± 716 minutes respectively

Allowing patients to grasp handrails for support during a treadmill stress test is often necessary. In this study subjects are discouraged from applying tension to their grip during the handrail assisted condition though this factor was not quantitated.

With the substantial reduction in oxygen cost and heart rate at any given submaximal load when using the handrail support one would expect to see an increase in exercise duration. When one considers the importance of duration in estimating oxygen cost from published tables, close attention should be paid to factors altering this parameter. Permitting handrail support also conflicts with the assumptions of Balke and Ware in calculating oxygen cost from treadmill speed and grade. The use of heart rate as an indicator of symptom onset and intensity when writing an exercise prescription is also adversely affected by such a support type protocol.

As a result of the data presented it is apparent that accurate determination of those values necessary for safe and effective prescription writing is not possible unless direct measurement is made or unless strict adherence to specified protocols is maintained. This appears to be of major importance when dealing with cardiac patients. In this study using healthy subjects the average error in prediction of $\dot{V}O_2$ when duration was used as the index was 17.5%. A average heart rate values showed a 9.5% deviation. Considering that these values were in the direction of indicating a greater capacity than really existed, serious attention should be paid to treadmill test protocol administration.

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the mitral valve and arrhythmias

Recently exaggerated and often unfounded diagnosis of prolapsed mitral valve with associated arrhythmias, especially atrial premature contractions, stimulates thought as to possible mechanism for the arrhythmias claimed to be related to prolapsed mitral valve leaflets. It is unlikely that tension alone, which is associated with the time course of rise in intraventricular pressure during systole, is responsible for even occasional premature contractions. The tension in the annulus cannot be any greater than ordinary. If there really is a cause-and-effect relationship, there must be another factor involved. Any explanation at this time can only be conjectural. To conjecture is permissible if the conjecture is at least thought provoking.

It is known that independent electric activity does exist in

muscle fibers of the mitral valve. Muscle fibers in the tricuspid valve leaflets have been shown to develop spontaneous action potentials in response to stretch and catecholamines. This same type of spontaneous action potential activity has been detected in the cardiac muscle fibers of the human mitral valve. In both reports, sustained rhythmic activity has also been described. Wit and Cranefield have found the electric activity of the cardiac muscle fibers in the pigtail monkey to be triggerable even with the development of sustained rhythmic activity. Verapamil will abolish this activity induced by catecholamines. Cranefield has described characteristics of the action potential trace.

Thus, it is possible that more arrhythmias may develop with disease and/or structural changes and hydraulic dysfunction

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Antithrombotic therapy for saphenous vein bypass grafts?

Closure of saphenous vein aortocoronary bypass grafts has been shown to occur in 19% of transplanted vessels within six months, although current occlusion rates are lower. Improved graft patency should increase the clinical benefits of this surgical procedure. It is possible that the isolation, preservation, and subsequent transplantation of an autologous segment of vein into the arterial circulation leads to endothelial damage which then sets the stage for thrombotic graft occlusion due to platelet accretion and/or fibrin deposition. Consequently we recently completed a randomized and controlled trial to determine whether anticoagulant or antiplatelet therapy would significantly reduce the incidence of vein graft thrombosis within six months of surgery.

In this study patients undergoing bypass grafting for coronary heart disease were randomly given oral anticoagulants (warfarin sodium), antiplatelet drugs (aspirin 300 mg and dipyridamole 75 mg three times daily) or no therapy and were evaluated for graft patency by coronary angiography six months later. An analysis after 50 patients were entered indicated no clinical benefit from these interventions and further that there was a greater than 90% certainty that continuing the trial would fail to improve graft patency rates in the treated groups.

Why did the antithrombotic therapy fail to improve graft patency? Perhaps the selected drugs were ineffective. Currently available antiplatelet agents seem to vary markedly in their pharmacology and spectrum of clinical utility. For example, sulfinpyrazone showed a distinct benefit in the Anturane Reinfarction Trial, but had no effect in reducing mortality in Canadian patients with transient ischemic attacks. Secondly, starting treatment three days after surgery may have been too late if thrombosis occurred just after graft implantation. Other investigators gave antiplatelet drugs prior to operation but were disheartened by excessive blood loss at surgery. Third, the dose of aspirin used in our trial may have been either too high or too frequent in light of the differential effects of aspirin on prostaglandin synthesis in endothelial cells and platelets. Fourth, technical or mechanical factors surrounding the implantation of the vein and poor blood flow in the graft due to distal coronary artery disease may be so thrombogenic that none of the currently available antithrombotic drug regimes will be effective. However, a recent abstract which outlined a study in which sulfinpyrazone was given to patients undergoing vein grafting provides a less pessimistic view. Finally, vein graft patency rates may have improved due to better surgical techniques so that an additional benefit

of pharmacologic therapy is difficult to show. For example, patency of vein grafts to the left anterior descending coronary artery in our study was 90%.

Even though our clinical trial showed no benefit from antithrombotic therapy, the results were still rewarding. If other information is available, patients should be spared unnecessary expense and risks of bleeding from anticoagulant or antiplatelet drugs given to improve graft patency.

Future studies could profitably be directed toward alternative protocols using antiplatelet agents in clinical trials. Particularly welcome would be the development and perfection of noninvasive techniques to assess platelet reactivity, graft patency, thereby sparing subjects the risks and efforts of repeated coronary angiography.

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A behavior pattern in men and the risk of MI. One might speculate that some feature of this pattern makes these men less likely to be light to moderate consumers of alcohol or alternatively that alcohol consumption may modify behavior patterns. The relation of Type A behavior pattern to alcohol intake is not clear and studies of behavior patterns and CHD have not included quantitative data on alcohol consumption. Some investigations have suggested that coronary event may be preceded by an increase in the number and severity of life changes although this association has not been found in all studies. Again it is possible that such life changes may alter alcohol consumption or themselves may be affected by use of alcohol. It is also necessary to consider alcohol as a dietary component and weigh the effects of alcohol consumption on the intake of other nutrients. This task is complicated both by continuing uncertainty over the role of diet in CHD and by the problems of measuring dietary intake in epidemiologic studies.

Understanding of the relationship of alcohol to CHD would be substantially advanced by studies considering the variables noted above. It would also be advantageous to have more data on the association in women. In addition the possibility of interactions between alcohol consumption and known risk factors for CHD such as cigarette smoking deserves investigation. The benefits and disadvantages of an agent are often best determined by a well-designed randomized treatment trial and after careful consideration of the ethical and practical issues, such an evaluation of alcohol consumption might well be informative.

Currently when advising patients concerning alcohol the emphasis should remain on the many documented adverse effects of excessive use of alcohol, including the risk of myocardial disease. We do not think that there is evidence at this time to claim preventive or therapeutic benefit for light to moderate use of alcohol for coronary disease. Caution is warranted both because our understanding of the relation of alcohol to CHD is insufficient for the reasons noted above and because the general problem of translating epidemiologic observations to therapeutic intervention applies especially to alcohol with its complex metabolic physiologic and psychologic effects. Even if one believes that the statistical association is causal, the words of Caelli seem well chosen: with 10 million alcoholics in this country we perhaps have a case for which the country is not yet ready.

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nificantly less than the control value. In spite of this the arterial blood pressure did not fall. It should be noted that the left ventricular stroke work index at exercise was significantly improved compared to the control value. Unlike the results following isoproterenol and hydralazine administration the patient did not demonstrate a resting tachycardia on either the initial catheterization or on follow up.

Diazoxide is a direct vasodilator that produces a secondary increase in cardiac output due to a decrease in the afterload in the pulmonary circulation. The increase in the cardiac output with diazoxide appears to be better than that seen with other vasodilators and may represent a direct inotropic action of the drug.

In summary the value of isoproterenol and oxygen therapy is limited while phenolamine, hydralazine and diazoxide show promise. Diazoxide would appear to have some advantages since it is the only drug out of the three that causes a significant decrease in the resting pulmonary artery pressures in addition to the decrease in pulmonary arteriolar resistance and increase in the cardiac output. Also since sudden death is an important feature of the syndrome the arrhythmogenic potential of resting tachycardia as seen with hydralazine must be considered.

The initiating cause for primary pulmonary hypertension may vary in each patient and therefore the response to these various medications may differ. Accordingly acute drug testing with these medications with later follow up may allow selection of the most appropriate drug in the individual patient. Certainly the results in our study and those of Wang and colleagues indicate that further evaluation of diazoxide in primary pulmonary hypertension is warranted.

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Of walking and dyspnea of congestive heart failure

The role of the veins in regulating the two cardiac pumps (right and left ventricles) and the flow of blood is frequently ignored. The veins are the great reservoirs of the body's blood. Much of the blood is stored in the legs. When people walk the venous pumps in the legs readily force blood toward the heart and into the lungs since there are no valves in the heart to prevent the returning blood from entering the lungs. This shifted volume of blood is returned to the systemic venous circulation and re-circulated there when the function of the two pumps is well balanced and synchronized. But when there is left ventricular congestive heart failure this synchronization and balance of the two pumps (right and left ventricles) is lacking and the blood shifted to the lungs tends to accumulate in the lungs and cannot be shifted back into the

tight systemic veins present in CHF. The blood is "stored" in the systemic veins as is true normally. Thus the pulmonary circulation remains over-engorged and the pressure within left ventricular CHF becomes quite elevated because of failure of the left ventricular pump and because of the pumping of blood or shifting of blood into the lungs by the venous pump in the legs upon walking or skeletal muscle contraction. The blood returning from the arterial system cannot accumulate sufficiently in the over-tight systemic veins so characteristic of CHF.

Physicians usually attribute the increase in dyspnea with development of dyspnea with walking (leg pressure) to the precipitation or worsening of left ventricular congestive heart failure as a result of the added work imposed on the heart.

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treatment for primary pulmonary hypertension

The exact mechanism for primary pulmonary hypertension is unknown. It is felt to be due to an inappropriate vasoconstriction of the pulmonary circulatory system. Postulated mechanisms of the increase in the pulmonary artery pressure and pressure characterizing this disorder include locally produced vasoconstricting substances as well as the possibility that the disease may be of autoimmune origin. The end result of whatever the initiating cause is a progressive increase in pulmonary vascular resistance with a concomitant and significant decrease in cardiac output resulting in symptoms of poor exercise tolerance and eventual right ventricular failure and sudden death. Most of the patients studied have been young females dying from the disease in an average of seven years.

In this regard, various vasodilators have been tried including tolazoline, acetylcholine, oxygen, and isoproterenol.¹⁻⁴ However, attempts to halt progress of the disease with these drugs have been unsuccessful.

Wassilak and colleagues reported a patient treated with tolazoline and phentolamine. The use of oxygen alone did not significantly lower the pulmonary artery pressure while he was awake. With the addition of phenoxybenzamine, the pulmonary artery pressure did decrease while the patient was asleep, but not while he was awake. However, the pulmonary artery resistance decreased to one-half the resting value. At follow-up one month and eight months later, the pulmonary artery pressure had returned to control values in spite of a continued decrease in the pulmonary vascular resistance. There is no mention of any change in the cardiac output. In a study involving six patients with primary pulmonary hypertension, Daoud and associates found that there was no consistent and predictable response to oxygen therapy. Therefore, the value of oxygen therapy by itself is doubtful.

Isoproterenol has been advocated by a number of others.⁵⁻⁷ The response to acute treatment with this agent is variable with only two out of six patients studied by Daoud and co-workers responding, and with only one patient with a response to sublingual isoproterenol. In this study, the symptoms continued to progress and required five hospitalizations for acute intravenous therapy. A patient studied by Shettigar and colleagues showed the same unfavorable response but then a later progression despite continued therapy. In both these studies, significant resting tachycardia was observed. Thus, the variable response to tachycardia, tachypnea, and repeated use of intravenous administration was seen to limit the usefulness of isoproterenol. Recently, there have been reports of the effectiveness of tolazoline,⁸ hydralazine,⁹ and dazoxone¹⁰ in primary

pulmonary hypertension. Phentolamine, both intravenously and orally, has been used by Ruskin and Hutter¹¹ to treat a patient with typical primary pulmonary hypertension. In their patient, intravenous and oral phentolamine both acutely and chronically failed to significantly reduce the resting pulmonary artery pressure and only moderately decreased the pulmonary vascular resistance. However, their patient demonstrated a significant and pronounced decrease in these indices with exercise, and this effect was well preserved when the patient was restudied six months later. In addition, there was a significant increase in the cardiac output at both rest and exercise. A recent report by Rubin and Peter¹² outlined their use with hydralazine in four patients. The pulmonary vascular resistance decreased both at rest and exercise with a concomitant increase in cardiac output. However, there was no significant decrease in pulmonary artery pressure at rest and late follow-up. All patients had a significant increase in the resting heart rate at rest. Thus, although hydralazine and phentolamine can decrease the pulmonary arteriolar resistance both acutely and chronically, the continued high pulmonary artery pressure may result in continued strain on the right ventricle and further progression of right ventricular failure. The patients in both studies improved symptomatically throughout the period of follow-up. Whether this will continue without further increase in the dosage of the medication remains to be seen.

Dazoxone has been used by both Wang and colleagues¹³ and by us¹⁴ with similar results. In our study, we administered intrapulmonary artery dazoxone to a young female who had both the clinical and objective findings of significant primary pulmonary hypertension. The pulmonary artery pressure fell from 63/30 (39) to 42/22 (28) with a concomitant decrease in the pulmonary arteriolar resistance from 430 dynes/sec/cm to 115 dynes/sec/cm. In association with this, there was a marked increase in the resting cardiac output from 4.8 L/minute to 10.4 L/minute. There was no significant tachycardia at rest. The patient was then placed on oral dazoxone 300 mg a day and was restudied six months later. During this period and since the follow-up catheterization, the patient has remained asymptomatic. At rest, the pulmonary artery pressure was 41/19 (27) and increased to 55/29 (38) with exercise. The pulmonary arteriolar resistance increased from 18.5 dynes/sec/cm to 19.0 dynes/sec/cm with exercise. Of significance was the fact that the cardiac output at rest remained high at 8.3 L/minute and increased significantly to 13.1 L/minute with exercise. Throughout the study, the systemic vascular resistance remained normal, although slightly

Correlation between exercise hemodynamics and increased magnitude of P terminal force

To the Editor

We have reviewed with interest the paper by Di Bianco and associates "Left atrial overload: A hemodynamic, echocardiographic, electrocardiographic and vectorcardiographic study" (*Am Heart J* 35:478, 1979).

Their results are similar to those of a study we have previously published but that was apparently overlooked by them. Our results were in general agreement with theirs except that we found a significant correlation between the PTF V and the exercise LA wedge pressure and not the resting LA wedge pressure. None of our patients had acute myocardial infarction and all had chronic stable angina. If patients with acute infarction are excluded it is likely that the resting PA wedge pressure may not correlate with the PTF V.

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- Shettigar U R, Barry W H and Hultgren H N. I wave analysis in ischemic heart disease—an echocardiographic hemodynamic and angiographic assessment. *Br Heart J* 39:891, 1977.

Reply

To the Editor

We would like to thank Drs Shettigar and Hultgren for bringing to our attention their published work. In patients with stable angina pectoris these authors demonstrated a correlation between the PTF V and the pulmonary artery wedge pressure during exercise but not at rest. Other findings in their study of patients with stable angina pectoris are supported by our evaluation of a broader patient group which included patients with acute myocardial infarction, primary myocardial disease and other disease entities. Both studies reveal the lack of correlation between hemodynamic measurements and echardiographically determined left atrial size or I wave duration. However, 11 of the 61 patients in our study had acute myocardial infarction and the question has been raised whether exclusion of this patient group might alter the significance of the correlation between the pulmonary capillary wedge pressure at rest and the PTF V. Review of our data reveals that 42 of 60 patients without acute myocardial infarction had a normal range of the pulmonary capillary wedge pressure and the PTF V as opposed to 9 of the 11 patients with acute myocardial infarction ($p = NS$). Pulmonary capillary wedge pressure and PTF V in patients without acute myocardial infarction ($n = 50$) were significantly

related ($r = 0.69 \pm 0.03$ SEM) this correlation did not differ from the overall group.

The hypothesis that chronic intermittent increases in left atrial pressure result in the increased magnitude of the P terminal force in Lead V in patients with ischemic heart disease is tenable. It seems clear that the surface electrocardiogram for whatever reason reflects alterations of intracardiac conduction time as was pointed out by Josephson and associates.

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Function testing soon after acute myocardial infarction

To the Editor

Recently Theroux and colleagues showed function in low level exercise stress testing performed before discharge after acute myocardial infarction (AMI) was a poor predictor of mortality in the subsequent year. They also can predict mortality in the subsequent year. Theroux and colleagues showed that the one year mortality rates were 11% in patients without changes in the ST segments and 20% in patients with depression of the ST segment ($p < 0.05$). Because of the prognostic value of this test, we were interested to learn how often a function test resulted in a change in management in patients recovering from an acute myocardial infarction.

We examined 82 sequential function tests performed on 40 male and 42 female patients of mean age 69.7 years (range 40 to 88 years) who achieved a mean MET level of 33 (range 17 to 11) on testing. Seventy three patients (89%) were recovering from an AMI six (7.3%) and the remaining three patients (3.7%) had suffered an acute ischemic episode. The mean days of study was hospital day 13.3 (range 1 to 21). For the AMI patients, hospital day 18.8 (range 10 to 34 days) for the AMI patients and hospital day 11.0 (range 1 to 14 days) for the acute ischemic episode patients. No morbidity or mortality was noted.

part by the exercise. Both the cardiac pump and the venous pump are mutually contributing factors, but the role of the venous pumps in the legs and other systemic veins must not be ignored in CHF. The role of the venous pumps must be considered when explaining the dyspnea and other clinical manifestations of CHF associated with walking.

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heart block. Unfortunately the skin overlying the box became necrotic and the pacemaker box had to be exchanged but the electrode could not be removed and was left in situ.

Nine months later the patient presented with pleuritic chest pain and screening showed that the abandoned electrode had migrated into the right ventricle and that the cut end of electrode had penetrated the free wall of the heart. He developed signs of pericardial tamponade and required an emergency thoracotomy at which time free blood was found in the pericardial sac. The redundant wire was removed and the patient made an excellent recovery.

This case re-emphasizes the need for secure fixation of the cut end of retained electrodes.

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Reply

To the Editor

We appreciate the interesting comments of Drs Perelman and Shui, whose case report on cardiac tamponade due to catheter perforation of the right ventricular free wall confirms the conclusions drawn in our recently published manuscript from similar experiences (AM HEART J 93:58, 1978).

However, we should like to point out that in our report case on catheter embolization into the pulmonary artery the electrode wire was not retrieved via thoracotomy as erroneously quoted by Drs Perelman and Shui but in fact had not left in situ since thoracotomy was refused by the patient who died suddenly several days later.

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Table 1

| | % of patients |
|---|---------------|
| New arrhythmia resulted in medication or change in medication | 5 |
| Chest pain resulted in change of medication | 4 |
| ST segment depression resulted in coronary angiogram | 4 |
| No new arrhythmia while on medication and therefore continued same | 3 |
| Chest pain resulted in a coronary angiogram | 2 |
| Blood pressure drop resulted in angiogram | 2 |
| Diminished exercise tolerance resulting in ordering a cardiac rehabilitation program not previously planned | 2 |
| Dizziness resulted in delay of discharge | 1 |
| Total | 31/8 (79%) |

The reasons for stopping the test were that the target heart rate was achieved in 41 patients (50%) symptoms of dyspnea, fatigue and leg weakness were seen in 21 patients (50%) chest pain was found in eight patients (9.8%) ST drop greater than 1.5 mm appeared in seven patients (8.5%) arrhythmias was found in three patients (3.7%) and a significant blood pressure drop was seen in two patients (2.4%).

We found that in 23 of the 67 patients (78%) the performing of a function test resulted in a change in the management of the patient by the attending physician. The reasons for a change in management by the attending physicians are shown in Table I.

Thus in addition to predicting prognosis function testing before hospital discharge resulted in a change in patient management in 78% of our patients. Function testing also allows an objective evaluation of a patient's response to low level exercise that he will experience in his home environment and allows the physician to more accurately determine the type of activities permissible for the patient at home. It also seems possible that in the future function testing may play an important role in determining which patients should have coronary angiography prior to discharge.

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- Theroux P, Waters D, D Halphen C, Debaux J, C and Mizgaza H. F. Prognostic value of exercise testing soon after myocardial infarction. *Engl J Med* 301: 341 1979.

Of bibliographies and medical librarians

To The Editor

This letter is written in response to the Annotation entitled "Of bibliographies." (*AM HEART J* 99:401 1980). The point made by Dr. George F. Burch that authors do not always research their topic adequately is well taken. As the editor of *AMERICAN HEART JOURNAL*, Dr. Burch is obviously in a position to observe the quality of literature research done by his colleagues. It is also true that a "careful review of the medical literature on any subject is an ordeal which is difficult and time-consuming. Our role as medical librarians is to aid those authors who do not have the time to do extensive research. If a physician feels that the Medline search is not adequate or preferred, most librarians will be happy to do a manual search and/or provide instruction so that the experience can be informative, educational and proper," as Dr. Burch suggests. Medical schools which include a segment on library/research orientations in their curricula are to be applauded for giving the student an appreciation of the literature.

Dr. Burch is incorrect however in thinking that Medline includes publications of only the past 5 years or so—the Medline data base includes citations from 1966 to the present.

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Reply

To the Editor

We thank Ms. Bury and Mr. Jones for their letter. On checking with our librarian we were informed that Medline has two types of services. The "current" Medline extends back three years, but service may be obtained as far back as 1966. It must be remembered however that many important contributions have been made prior to 1966. Unfortunately a review of the literature beyond 1966 is very time consuming.

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Migration of redundant pacing electrode

To the Editor

Retting and associates recently described a case of migration of a redundant transvenous pacing electrode (*AM HEART J* 99: 587 1979). In their case the electrode settled in the pulmonary artery and was retrieved via a thoracotomy.

We have had a similar experience but with a more serious consequence. The patient, a 74-year-old man, required permanent pacemaker because of Stokes-Adams attacks due to complete

Association for Advancement of Behavior Therapy

The 14th annual convention of the Association for Advancement of Behavior Therapy will be held on November 20 through 23 1980 at the New York Hilton New York City. Included will be five sections of the 8 hour basic course in Clinical Behavior Therapy 12 pre convention institutes lasting 5 hours and limited to 30 participants and 40 workshops lasting 3 hours and limited to 12 attendees. In addition there will be symposia panel discussions invited addresses and poster board sessions all presented by experienced professionals in the field.

For further information regarding this convention contact Steven C Hayes PhD Program Chairperson Association for the Advancement of Behavior Therapy 490 Lexington Ave New York N Y 10170 Telephone (212) 682 0066.

Europacing 81

The Second European Symposium on Cardiac Pacing will be held in Florence Italy on May 4th through 6 1981. The symposium is organized by the European Working Group on Cardiac Pacing in cooperation with the Italian Pacing Association. Professor G A Feruglio is chairman of the organizing committee. For further information regarding this symposium contact The Secretariat Europacing 81 O I C Organizzazione Congressi Via C Modena 19 50121 Firenze (Florence) Italy.

Third World Congress on Pain

The Third World Congress on Pain sponsored by the International Association for the Study of Pain will be held on September 4 through 11 1981 in Edinburgh Scotland. For further information contact Third World Congress on Pain University of Edinburgh Centre for Industrial Consultancy and Liaison 16 George Sq Edinburgh, EH19 9LD Scotland, United Kingdom or Louisa F Jones MS FRCR Secretary Secretary International Association for the Study of Pain Dept of Anaesthesiology RN 10 University of Washington, Seattle Wash 98195.

Workshops in Interventional Radiology

The Division of Cardiovascular Radiology Department of Radiology Johns Hopkins University School of Medicine will sponsor a series of one day workshops in interventional radiology. Intensive teaching to small groups will be provided in vascular embolization procedures percutaneous biliary drainage and transluminal angioplasty. Workshops will be conducted on Saturday December 11 1980 and on Saturday February 7 1981. The number of course participants is limited to 20. Workshops are approved for 4 hours of Category I credit. For information and application forms please contact Klemens H Barth MD Director Interventional Radiology Workshop The Johns Hopkins Hospital Baltimore MD 21205 Telephone (301) 955 6728.

Book reviews

Interpreting the Electrocardiogram By James C. Fleming
New York 1979 Update Publishing International Inc. 13.
pages.

This is an atlas type book designed to teach physicians how to interpret electrocardiograms. The technique used is to teach the student how to interpret patterns i.e. in memorization patterns without much knowledge of the fundamentals of electrocardiology. The fundamental aspects of electrocardiology and electrophysiology are not discussed. The book is presented in such a manner that the reader need not have a knowledge of membrane potentials or the electric activation of the myocardium or the phenomenon of reversion. This book should prove useful to nurses and paramedical personnel who wish to have a practical knowledge of the patterns of electrocardiography. The diagrams are many and simple and the tracings are well chosen.

Cardiovascular Physiology III Volume 18 Edited by A. C. Guyton and D. B. Young Baltimore 1978 University Park Press. 368 pages. Price \$14.50.

This is another excellent issue of *International Review of Physiology* which is concerned with cardiovascular physiology. The contributors have condensed for the reader the new findings of interest in the field of cardiovascular physiology. The selected in situ sections include contraction and relaxation of the myocardium, determinants of systemic blood flow, reflex control of vascular capacitance and skeletal muscle circulation, transcapillary transport of small solutes and water, interstitial lymphatic flow system, pulmonary and capillary exchange and pulmonary edema and cardiogenic hypertension. The more recent publications of data are well oriented with physiological studies repeated in the more remote past. Anyone involved in cardiovascular physiology and training and teaching of clinical cardiovascular problems will find this publication to be a stimulating and thought provoking source of important material. This review is quite different from most annual reviews in any field of medicine in that the reports are presented as an organized review of the respective subjects. The editors and contributors have produced a valuable publication.

Coronary Heart Disease Third International Symposium Frankfurt Edited by Martin Kaltenbach M.D. Paul Lehtinen M.D. Raphael Balcon M.D. and Wolf Dirk Buysman M.D. Acton Mass. 1978 PSG Publishing Company. 346 pages. Price \$41.00.

This report on coronary heart disease includes the presentation, and discussion at the Third International Symposium held in Frankfurt during February, 1978. The many short papers are divided into eight parts. Part I related to coronary collaterals is of particular interest not only to physiologists and anatomists but to clinicians as well. The importance of the collateral circulation in ischemic heart disease is nicely presented. Part 5 is devoted to discussion of coronary spasm, a subject known to be important in cardiology for many years, but of considerable interest in clinical research at present. The

clinical importance of coronary spasm is well discussed by investigators directly interested in the problem. Part 7 is devoted to the mechanical treatment of ischemic disease. This part should interest all physicians who treat ischemic heart disease. The entire publication is of considerable interest and value. This book is highly recommended. It is easy to read, the illustrations and tables are good and the discussions are of interest to anyone who manages patients with coronary artery disease. This is an excellent book that can best be appreciated by critical reading and study.

Ambulatory Electrocardiography By Edward H. Chung New York 1979 Springer Verlag. 241 pages. Price \$14.90.

This book is intended for training in the use of Holter monitoring in the management of cardiac disease. Chung has briefly outlined the indications, applications in diagnosis, interpretation, record or protocol keeping by the patient and clinical problems for which it is most useful. These discussions are followed by 100 case histories and segments of recordings with interpretations. The book is primarily an atlas for beginners to learn how to employ Holter monitoring in the practice of cardiology. This is a good book with its primary purpose achieved. The reader who is not acquainted with this procedure will find the 100 case examples interesting and challenging even to cardiologists. It is not possible to critically review each case presented. This must be left to the readers. Nevertheless, Case 36, page 8, of a supraventricular tachycardia has two questions presented by the author to his readers. One is "What is the treatment of choice?" How can this question be answered without the entire clinical data. Cases like this do challenge a thoughtful critical reader. This is a good book which should interest beginners as a supplement to other literature on cardiac arrhythmias.

Myocardial Infarction second edition By Art Louis Goldberger St. Louis 1979 The C.V. Mosby Company. 276 pages. Price \$26.50.

This second edition attests to the success of the first edition. The author has added new information to assist the clinician in continuing his training in electrocardiography with emphasis on the ECG diagnostic manifestations of myocardial infarction. The author is the son of Dr. Emanuel Goldberger who introduced the augmented limb leads to clinical electrocardiography. The book is divided into two parts. Part one is concerned with depolarization (Q wave) pattern simulating myocardial infarction and part two is concerned with repolarization (ST-T) patterns simulating myocardial infarction. It is a good book which clearly presents the problems in differential diagnosis of myocardial infarction by ECG. Physicians in training will find a critical study of this book to be a valuable effort. The ECG remains of paramount importance in clinical cardiology. Goldberger has selected good illustrations and included a good bibliography of 64 well selected references. Myocardial infarction is an important and common problem in the practice of medicine and the ECG is of routine use in diagnosis and management. This is a good addition to the medical literature.

leisure to pursue full time academic and scholarly activities. Scholarship has lessened because clinical duties are too time consuming and demanding. Teaching suffers and the fundamentals of medical science and the depth of critical discussions, self criticism and self evaluation are at a minimum. In spite of large clinics and large hospitals and capable physicians outside the schools, the medical schools are in private practice and in competition with the private practitioners and private clinics, bearing the burden of large budgetary problems and ever demanding large salaries of the clinical faculty and private patient care. This should not be.

Thus with critical review it becomes evident that we have reverted back to 1910 in medical education. How did this happen? Is it good? Where are the certifying groups who review full time medical schools? Why isn't medical education being critically reviewed in 1980 with scholarship and teaching and research being made the premium for dedicated scholars and scientists in medical schools, people with missionary dedication to scholarly pursuits?

Outstanding teaching and training of physicians can be done only with strictly full time clinical faculty dedicated to scholarship, teaching and research—a faculty willing to accept a financial sacrifice in exchange for opportunities to study, think, teach and do research on a full time basis without an excessive burden of primary patient service responsibilities. Sufficient people exist in medicine to provide such a faculty for all medical schools of America. In 1910 a change to full time faculty developed with success. This can also occur in 1980 if the various administrations in the U.S. and the American people wish and are willing to bear the financial burden involved.

Many more medical schools with small classes and highly motivated, truly full time faculties must be the objective of medical education in America for the immediate future. We need at

least 300 more medical schools with small student bodies and with excellent teachers in which the objective is to provide the best medicine for the people of America and in which earning money is not paramount. The scholars of medical schools, students and faculty should be expected to give money and must not be concerned with earning money. They must be concerned with training, administering to the sick, emphasizing preventive medicine regardless of economic or social status of the patients. The people of America will be the winner in the end and therefore the people must provide the support without restrictions—but not by direct or indirect payment for services (fee for service) to a so called full time clinical faculty. The American people will benefit from the support through the improved services of better trained graduates who eventually enter private practice and become the full time private physicians of the people. It takes time to teach and advance knowledge and it takes time to practice good medicine and care for the sick. When the two types of medical endeavors are attempted simultaneously by the same people, both usually suffer from poor performance and certainly suffer from inadequate time for thought, scholarship, teaching and learning.

Let us re-emerge in 1980 as we emerged in 1910 with true and strictly full time clinical faculties and medical schools of scholars—faculties and students interested only in learning, studying, thinking and venture research. Let the physicians in private practice care for the sick on a fee for service basis. A volunteer faculty should exist but a strictly full time faculty dedicated to scholarship, teaching and research should constitute the core of the medical schools.

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Editorials

Of 1910

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The Flexner report¹ appeared in 1910 marking the beginning of significant improvement in medical education in the USA. In 1910 there were many poor medical schools in which earning money was an important objective of the clinicians who owned the schools and controlled the hospitals. Preclinical faculty was hired by these clinicians. The faculties were not considered full time since they practiced private medicine to earn money for themselves. Scholarship science and research and investigation into the unknown were essentially non-existent. Students who paid their tuition were essentially assured a diploma. The Flexner committee exposed the inadequate medical education and recommended drastic changes, especially, the need for full time clinical faculty that would be concerned with teaching, research and scholarship and not with the private practice of medicine. In fact the full time faculty was definitely not to practice medicine privately. The faculty was to teach good medicine and to search into the unknown through research, thought and discourse for the sake of advancing knowledge. The strictly full time clinical faculty was to produce outstanding physicians to render care of the sick with concern for the sick according to performance, background and model established by the full time clinical teachers dedicated to scholarship. The full time clinical faculties were

rapidly instituted after the Flexner report was published. The medical schools displayed pride and extreme satisfaction with their full time clinical faculty and their accomplishments. The level of academic performance and rating of each medical school were determined by size and quality of the strictly full time faculty, with reward for the best clinical scholars. Any clinical faculty appointee with patient service responsibility and fee for service no matter how arranged was considered a part time and not a full time faculty member. Even geographic full time appointment was not permitted at the outset. Those who were interested in private practice joined the part time clinical faculty and made important contributions to their respective medical schools.

We are now in 1980 but back to the level of 1910 in medical education. We have been there for several years, a transition which started 20 or more years ago. The earning of money is now a strong motivation and an overly emphasized objective and concern of teaching medical institutions. At present the universities and medical centers own the faculty, the hospitals and the clinics. The size of the hospital, number of patients and funds earned seem to reflect important qualities of achievement—the same qualities which are considered a great achievement in private non-academic clinics. Budgets must be met and the magnitude of salaries is the index of success and faculty satisfaction. The clinical faculties are now busy practicing medicine to earn money for the medical schools so the schools can meet these budgets and pay salaries including their own. The faculties no longer are free and at

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the epicardial and body surface ECG could be demonstrated which invalidated the earlier conclusions Durrer and associates² reported that even an SEI of extremely small size (1 cm in diameter) can lead to abnormal Q waves. The 1957 report from Prinzmetal's laboratory and Durrer's studies are in full agreement with practically all later autopsy reports on the ECG in SEI. Abnormal Q waves can be found in most SEI and TMI cases but they may be absent in a substantial number of infarcts of both types.

Scher³ has been one of the few investigators who took notice of the changing concepts in Prinzmetal's laboratory. In his excellent review on the Excitation of the Heart in 1962 he stated: "The work of Prinzmetal and his colleagues deserves some comment. All of the early papers in a very large series stressed the fact that most of the inner layers of the wall were silent and were depolarized before the beginning of the peripheral electrocardiogram." A final paper in the series re-examined the major claim (excitation of inner layers before the beginning of QRS) and found it to be incorrect. It appears truly amazing that in the relatively short interval of three years between the first and second report from Prinzmetal's laboratory, an erroneous concept could become so deeply ingrained in cardiologists' thinking.

At this point in time one is tempted to conclude that no matter how many additional autopsy studies refuting the concept of the silent SEI will be published in the next decades, the public at large will probably take little or no notice. We have no real explanation for the persistence of this concept which could have been abandoned in the late fifties. It may be related to the shifting emphasis toward many other investigative procedures such as coronary angiography, ventriculography, and others, and may from postmortem studies which used to be and still remain the most essential objective evidence for the presence or absence of infarction. The fact remains that both TMI and SEI can be found in substantial numbers without typical Q wave abnormalities. The electrocardiogram alone seems to be of little help in the differentiation between these two types of infarct.

Many reasons have been given for the absence of Q wave abnormalities in certain patients with MI. The presence of multiple infarcts, MI location in certain regions of the left ventricle which

are relatively silent⁴ and changes in the middle or late part of the QRS are some explanations which have been offered. A detailed discussion goes beyond the scope of this editorial.

Differentiation between TMI and SEI is only of academic interest because it was for some investigators that there might be a difference in the clinical course and prognosis. Patients having SEI or TMI cases with SEI believed to have a more benign course. Comparisons were made, therefore, between SEI patients with QRS abnormalities and others with ST-T changes only.⁵ No autopsy confirmation on infarct size and extension within the ventricular wall was available. From the discussion it should have become clear that if patients could have had TMI or SEI. To our surprise, no significant differences in the clinical course and prognosis could be found.

It is not inconceivable that patients with subendocardial lesions might have a better prognosis than those with TMI. With present electrocardiographic techniques a differentiation between SEI and TMI does not appear feasible. However, in addition to the relative location within the left ventricular wall for prognosis, one has also to consider the total muscle mass which has become necrotic. Many subendocardial infarcts are very large and almost circumscribing like and the total amount of dead tissue in these cases is substantial.⁶ More detailed correlations between enzyme levels and ECG changes might lead to better clues for estimating infarct size.

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"Silent" subendocardial infarcts fact or fiction?

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During the last 25 years it has become customary to make a distinction between electrocardiograms which are considered compatible with subendocardial infarcts (SEI) and transmural infarcts (TMI). The former are believed to lead only to ST and T wave changes whereas QRS changes and more specifically the development of abnormal Q waves are considered characteristic for TMI. According to this concept the subendocardium is electrocardiographically silent as far as the QRS complex is concerned.

The vast majority of autopsy correlations reported in the literature are in disagreement with this simplistic concept. In most recent years Savage and associates, Sullivan and colleagues, and Raunio and co workers reported in great detail on a total of 154 autopsies and their ECG findings prior to the patients' death. There appears to be general agreement between these investigators that the majority of cases with SEI exhibit typical QRS changes and furthermore that in a substantial number of patients with TMI the characteristic Q wave changes cannot be found. Raunio and co workers reported only very recently in the August 1979 issue of *THIS JOURNAL* on a new series of 80 autopsies. In this very carefully executed study 53% of the SEI cases showed QRS changes which were typical for myocardial infarct (MI). Similar QRS changes were present in 65% of the TMI patients; a difference which is hardly significant.

Savage and associates¹ found 11 SEI cases in their autopsy series of 24. Ten out of these or 81% could be diagnosed as infarct on the basis of typical QRS changes and only one case with a posterior SEI had no abnormal Q waves in Leads II, III or a V_r. Abbott and Scheinman reported on 230 patients with acute MI. In 78 or 34% of these cases the electrocardiogram did not show signs which are considered diagnostic for MI. Eight cases of the latter group came to autopsy and all of them were found to have TMI.

The literature on ECG findings in autopsy proven SEI and TMI cases has been reviewed recently very extensively by Savage and colleagues¹ and by Raunio and co workers.² The history goes back to Wilson and associates who described typical Q wave changes with SEI both in animals and in men.³ There appears to be overwhelming evidence that most SEI cases show Q wave abnormalities which are typical for MI. Furthermore the percentage of SEI cases which do not exhibit characteristic Q wave changes appears to be very similar to that of TMI cases without Q wave abnormalities. To distinguish between SEI and TMI on the basis of the electrocardiogram seems therefore not possible.

How then did the ECG differentiation between these two types of infarcts develop? The work which is most often quoted is that of Prinzmetal and associates⁴ who reported in 1954 on experiments in seven dogs with chronic SEI and on twelve dogs with acute SEI. From their results they concluded that subendocardial depolarization is silent and thus should not affect the electrocardiogram. In a later study from Prinzmetal's laboratory in 1957 when more refined recording techniques had become available a significant contribution of the subendocardium to

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Evaluation of contractile state of the left ventricle from the peak of the first derivative of the apexcardiogram

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Johnston and Overy¹ were the first to report that the magnitude of the first derivative of the apexcardiogram (dA/dt) was in close relation to the contractile state of the myocardium. Some authors²⁻⁴ using suitable mechanical calibrating devices determined left ventricular wall velocity and other quantitative indexes from the height of dA/dt . Because of the difference among individual subjects in cardiac size and body build, quantitation of left ventricular wall velocity has not been feasible by this method.^{5,6}

Reale⁷ proposed an alternative approach of using the first derivative of the apexcardiogram. He established the similarity between the interval from the onset of ventricular depolarization and the peak of the first derivative of the apexcardiogram on one hand and the interval from the R wave of the electrocardiogram to the peak dP/dt , on the other hand as suggested by Mason and colleagues.⁸

In order to maintain the informative value of the height of the peak dA/dt and avoid the calibrating difficulties we proposed a new way of interpreting the peak dA/dt . The amplitude of the peak dA/dt was expressed as a percent of the total deflection of the first derivative of the apexcardiogram.

The present study was designed to assess the clinical value of measuring the peak of the first derivative of the apexcardiogram (1) by defining

the normal values of the ratio of peak dA/dt to the duration of the interval from ventricular depolarization to peak dA/dt (R to peak dA/dt) (2) by investigating the effect of different pharmacologically induced variations in the contractile state of the human myocardium on the above parameters and (3) by comparing patients with unpaired left ventricular function with controls.

Subjects and methods

A left apexcardiogram and its first derivative were obtained in 104 individuals—50 normal subjects ranging in age from 20 to 61 years (mean 38 ± 14 years) and 38 patients with ischemic heart disease ranging in age from 30 to 73 years (mean age 51 ± 16 years). In 16 additional subjects the effect of pharmacological agents with positive and negative inotropic action was studied.

In the group of normal subjects no previous history of heart disease was presented and a complete physical examination, 12 lead electrocardiogram, carotid pulse tracing, apexcardiogram and chest x-ray were normal.

The patients with ischemic heart disease had a history of old myocardial infarction—6 months to 12 years after onset. Their diagnosis was based on typical anamnestic data, electrocardiographic examinations and increased enzyme activity in the acute phase. When investigations were performed all patients suffered from decompensated coronary artery disease (degree of decompensation Class I to II according to the criteria of the New York Heart Association). Not included in the study were the patients on digitalis and antiarrhythmic agents and patients with beta-block.

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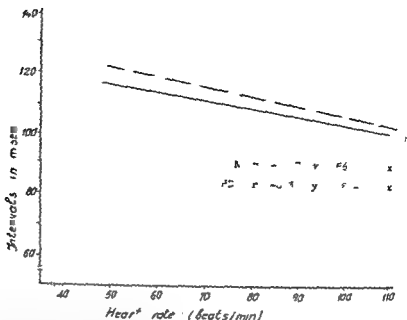


Fig 2 Linear regression analysis between interval R to peak dA/dt and resting heart rate in normal subjects (N) and in patients with ischemic heart disease (IHD)

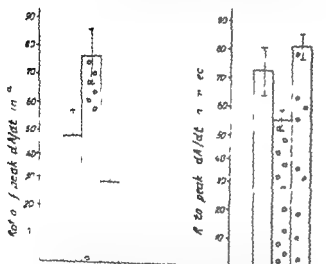


Fig 3 Mean changes in the average values of ratio of peak to total amplitude (dA/dt) (left) and interval R to peak dA/dt (right) at rest (plain bar) after beta adrenergic stimulation (bar with open circles) and after beta adrenergic blockade (bar with solid circles). Each bar represents the mean \pm SD

-29 ± 15 ($p < 0.001$) and the interval R to peak dA/dt was increased by 9 ± 6 msec ($p < 0.02$) (Figs 3 and 4).

In the patients with ischemic heart disease a decrease of the ratio of the peak dA/dt occurred and its mean value amounted to $32 \pm 13\%$ ($p < 0.001$). In the same patients an elongation of the interval R to peak dA/dt with a mean value 121 ± 15 msec ($p < 0.01$) was also found.

Discussion

Although the exact genesis of the apexcardiogram is not clearly understood many observations indicate that the configuration throughout the course, the height and the slope (especially in the isometric phase) of the apexcardiogram are significantly correlated with left ventricular pressure.¹⁻⁴ Reale¹ reported the similarity in time and contour between the first derivative of the left ventricular pressure and the first derivative of the apexcardiogram. It was shown in experimental studies^{5,6} and clinically⁷ that correlation between the first derivative of the apexcardiogram and left ventricular pressure during hemodynamic changes was fairly good. All the authors used a calibrating device when determining the height of the first derivative of the apexcardiogram and expressed its value in different units—mm Hg/sec,¹ %/sec,² or g/sec.³

Quantitation of peak dA/dt by use of an absolute value of amplitude have been rare because of differences among individual subjects in cardiac size and thoracic shape.⁸ Owing to the difficulties in calibrating the sensing device and therefore in assessing units of measurement of the first derivative of the apexcardiogram we examined the relative height of the peak of dA/dt as percent of the total amplitude of the first derivative.

Our data for parallel modifications of the ratio of peak dA/dt after pharmacologically induced

Pharmacological interventions were performed in 16 volunteers in order to study the effect of positive and negative inotropic drugs on the first derivative of the apexcardiogram. Isoprenaline infused intravenously at a rate of 0.003 $\mu\text{g}/\text{kg}/\text{minute}$ and propranolol (Obsidan GDR) 5 mg intravenously were given in order to obtain the appropriate effect. Informed consent was obtained from the subjects prior to the examination.

The polygraphic tracing was performed by rotating recumbent subjects 30 to 50 degrees toward the left lateral decubitus position. Apexcardiograms were recorded by means of a piezo electric transducer (RFT GDR) with an infinite time constant. The transducer was held by a circumferential adhesive strap at the point of maximal impulse of the apex beat of the heart.

The first derivative of the apexcardiogram was obtained by passing the pulse wave of the apexcardiogram through a resistance capacitance (RC) network differentiator. The differentiator was constructed in our laboratory and consists of a low pass filter followed by a high pass filter both filters having the same time constant (0.1 msec) with a flat response in a range of 0 to 80 Hz. The attenuation of the differentiator is down -20 db per decade. Thus high frequencies are accentuated and low frequencies are attenuated.

During mild expiratory apnea simultaneous records were made of the electrocardiogram, phonocardiogram, apexcardiogram and dA/dt on a six channel recorder (6 NEK 3 GDR). Paper speed was 100 mm/sec.

Analysis of the simultaneous tracings (Fig 1)

1. Ratio of positive amplitude to total amplitude of the first derivative of the apexcardiogram expressed as a percent of total deflection.

2. Interval from R of the electrocardiogram to the peak of the first derivative of the apexcardiogram (R to peak dA/dt). This interval was corrected for heart rate by formulas from regression analysis in Fig 2 which represents the relation between heart rate and survival R to peak dA/dt in normals and in patients with ischemic heart disease.

Results

In the control group the mean ratio of the height of the peak dA/dt was $48 \pm 14\%$ of the total deflection of the first derivative of the

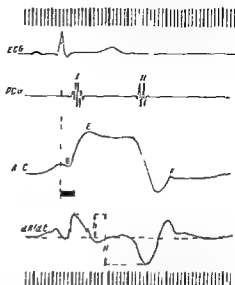


Fig 1 Simultaneous recordings of electrocardiogram (ECG), phonocardiogram (PCG), apexcardiogram (ACG) and first derivative of apexcardiogram (dA/dt). Blackened area denotes the interval from R wave of ECG to peak dA/dt . I denotes the peak amplitude of dA/dt and H represents the total amplitude of dA/dt . The vertical lines determined 0.02 sec intervals.

apexcardiogram. The interval from R of the electrocardiogram to the peak of the dA/dt was 73 ± 15 msec.

To evaluate the possible influence of resting heart rate on interval R to peak dA/dt a linear regression analysis of the first variable with the latter was carried out in the 56 normal subjects and in 38 patients with ischemic heart disease. There was some tendency of interval R to peak dA/dt to decrease at increasing resting heart rate (Fig 2) however the inverse correlation was very slight although significant (normal subjects $r = -0.37$ $p < 0.01$ ischemic heart disease $r = -0.39$ $p < 0.01$).

Sixteen young adult men with no cardiac disease submitted to intravenous injection of isoprenaline. The ratio of peak to total amplitude (dA/dt) showed augmentation and its mean value amounted to $81 \pm 16\%$ whereas the mean basal value was $49 \pm 15\%$ ($p < 0.001$); moreover the interval R to peak dA/dt was reduced by -16 ± 5 msec ($p < 0.001$). In the same subgroup a determination repeated after the infusion was stopped showed parallel returns of the above parameters toward perfusion levels. Following beta adrenergic blockade with propranolol the mean ratio of peak to total amplitude was diminished to

Summary

Simultaneous records of the electrocardiogram, phonocardiogram, apexcardiogram (ACG), and the first derivative of the apexcardiogram (dA/dt) were obtained in 50 normal subjects and in 38 patients with ischemic heart disease. This allowed us to measure the ratio of peak dA/dt to total amplitude of the first derivative in percent and the interval from electrical stimulation to peak dA/dt (R to peak dA/dt). In 16 additional normal subjects the effects of pharmacological agents with positive and negative inotropic action were studied with the above parameters. During isoprenaline infusion the ratio of peak to total amplitude dA/dt was increased and the interval R to peak dA/dt was shortened, while after propranolol the ratio of peak dA/dt diminished and the interval R to peak dA/dt showed elongation.

In normal subjects the ratio of peak dA/dt averaged $48 \pm 14\%$ and it was significantly lower in patients with ischemic heart disease ($32 \pm 13\%$, $p < 0.001$). In controls the interval R to peak dA/dt was 73 ± 15 msec, whereas in ischemic heart disease it showed elongation (121 ± 15 msec, $p < 0.001$).

It is concluded that the ratio peak dA/dt and the interval R to peak dA/dt expressing noninvasively the rate of pressure changes and the duration of the development of maximum tension during isovolumic contraction provide useful information on left ventricular function.

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IMPORTANT INFORMATION FOR AUTHORS

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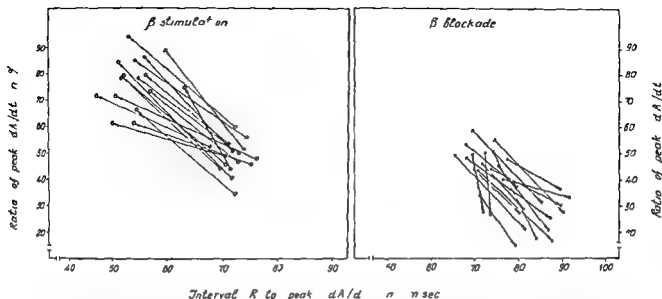


Fig 4 Variations of the ratio of the peak of the first derivative of the apexcardiogram to total derivative expressed as a percent and interval R to peak dA/dt expressed in msec during isoprenaline infusion and after propranolol. The arrows point to values obtained after pharmacological intervention. There is a strong reciprocal correlation between changes in the height of the peak dA/dt and the interval R to peak dA/dt . The near parallelism of the curves indicates similar rates of change for both factors in all patients.

variation in the contractile state was confirmed with similar methods. Mason and colleagues¹ found that when the myocardial contractile state was enhanced by isoprenaline infusion there was an evaluation of peak dp/dt . Conversely when contractility was depressed by beta adrenergic blockade most patients showed a lower peak dp/dt .

The precise experiments in dogs by Willemss and colleagues² during the effects of different interventions established the changes in amplitude of the calibrated dA/dt expressed as a percent of the controls. They found a 60% elevation of the dA/dt provoked by isoprenaline and a decrease by 40% after propranolol. Denef and associates³ reported that in dogs positive inotropic interventions provoked a marked increase in peak dA/dt whereas negative inotropic agents had the opposite effect. Furthermore they found a fairly good correlation between these changes and changes of left ventricular dp/dt after the same pharmacological interventions. Similar results were obtained clinically.⁴

Mason and co-workers⁵ measured the interval from electrical stimulation to peak dp/dt and assumed that it expressed the duration of the development of maximal tension in the ventricle. They found that the same interval was inversely

related to the contractile state in the isolated muscle strip and also that it was independent of preload and afterload. Several authors^{6,7,8} investigated the interval from the onset of ventricular depolarization to the peak of the first derivative of the apexcardiogram and found that the interval R to peak dA/dt has the same significance as the interval R to peak dp/dt . It has been demonstrated that the interval R to peak dA/dt increased after beta adrenergic blockade⁹ and shortened when the patient was given a beta adrenergic agonist.^{10,11} Other authors established an elongation of the same interval in patients with left ventricular failure due to atherosclerotic coronary heart disease and a close correlation between the interval R to peak dA/dt and the ejection fraction.¹²

In conclusion our findings relative to changes of the interval R to peak dA/dt are in agreement with the investigations of several authors.¹³ The proposed ratio of peak dA/dt to total amplitude of the derivative avoid the difficulties in calibrating the apexcardiogram and its first time derivative and simultaneously using the ratio of peak dA/dt and interval R to peak dA/dt permits a more complete noninvasive evaluation of the contractile state of the left ventricle from the peak dA/dt .

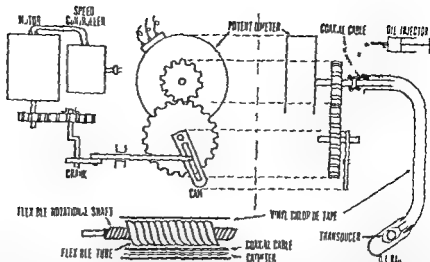


Fig 1 Diagrammatic illustration of the transesophageal sector scanner. A small transducer in the esophagus is alternately rotated by a flexible rotational shaft and motor at 6 to 25 Hz (12 to 50 fields/sec). Although the small transducer is rotated alternately with great speed, there is little movement of the external flexible tube or oil bag, minimizing irritation or trauma to the esophagus.

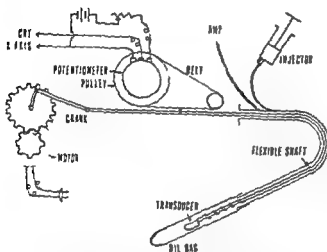


Fig 2 Diagrammatic illustration of the transesophageal linear scanner. A small transducer in the esophagus is moved up and down by the flexible shaft and motor at 4 to 10 Hz (8 to 20 fields/sec).

continuously by phase control of alternating voltage using thyristors. Maximum selective pulse repetition frequency is 60 KHz. The field of view varies in depth from 10 cm to 17 cm according to the pulse repetition frequency. The sector angle varies from 60 degrees to 180 degrees by changing a connecting point of a cam (Fig 1). Thus horizontal images of the entire adult heart can be obtained with this scanner. Although the transducer is rotated at a high frequency, the external flexible tube is stable within the esophagus. Moreover, the enveloping oil bag minimizes trauma to

the esophagus (Fig 1). To identify the echo source of the cross sectional image a particular scan line is manually selected and M mode is switched to M mode to obtain M mode esophageal echograms.

Linear scanner In order to obtain vertical images of the heart, a transesophageal mechanical linear scanner was developed. Fig 2 shows a diagram of the linear scanner. A small transducer (transducer specifications as in the transesophageal sector scanner) is moved up and down in the esophagus by a flexible shaft and a motor at a rate of 4 to 10 Hz. The plane of the scan is vertical through the center of the esophagus. As shown in Fig 2, a potentiometer is rotated simultaneously with the transducer and monitors its position. The signals detected by the transducer are amplified and displayed on a CRT as B-mode. That the position of an individual scan line corresponds exactly to the position of the transducer at the same instant. Thus vertical cross-sectional heart images are displayed in rectangular format on a CRT at a rate of 8 to 20 fields/sec. The movement of the transducer can be varied from 2.5 cm to 8 cm by changing the crank and repetition frequency, and depth of field are as in the sector scanner.

Recording methods A Polaroid camera, a 35 mm still camera, 8 mm movie camera, and a 16 mm movie camera can be utilized for the recording.

Examination technique This system was evaluated

Transesophageal cross-sectional echocardiography

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Real time cross sectional echocardiography has proven useful for diagnosis of certain cardiac diseases and several imaging systems have been developed.¹⁻³ However because the heart is observed through a small echo window on the chest wall the area which can be observed is considerably restricted. In addition it is sometimes difficult to obtain heart images of diagnostic quality in patients with chronic obstructive pulmonary diseases barrel chest and obesity. In order to minimize these limitations and to observe a wider area of the heart we developed a transesophageal high speed scanning system which can obtain cross sectional heart images without hindrance from ribs sternum and lung

Methods

The scanning system employs two kinds of hand held mechanical scanners each having a flexible tube and small ultrasonic transducer contained within a small oil bag which allows easy swallowing by adults. One is a sector scanner which obtains horizontal images of the heart and the other is a linear scanner which obtains vertical images of the heart. These scanners are used in conjunction with an improved Toshiba SSL 51H system which was originally developed as a transthoracic wall mechanical sector scanner.

Sector scanner The sector scanner consists of a motor (single phase commutator type) which can control the speed of rotation an iron flexible tube containing a flexible rotational shaft and a small transducer which is enclosed in an oil bag (15 mm diameter) (Fig 1). The specifications of the transducer are 2.25 MHz or 3.5 MHz 10 mm diameter and 7.5 cm focus. The transducer is mounted in a 12 mm by 20 mm by 6 mm casing with rounded edges for easy esophageal passage, and is positioned at the tip of the flexible rotational shaft. The flexible rotational shaft is enclosed in the iron flexible tube which has a diameter of approximately 8 mm and the latter is then wrapped with vinyl chloride tape. The patients can easily swallow the flexible tube and shaft. The oil bag which covers the transducer can be filled with oil by means of an injector. The small transducer in the esophagus is rotated alternately by the flexible rotational shaft and the motor at a rate of 6 to 25 Hz. The ultrasonic beam is alternately swept to the left and to the right so that the plane of the scan is perpendicular to the esophagus and the resultant images are displayed in a circular format. The position of the transducer in the esophagus is continuously detected by a potentiometer which is connected directly to the flexible rotational shaft. The signals of reflected echoes are displayed on a cathode ray tube (CRT) as B mode so that the angle of an individual scanning line is equal to the angle of the transducer at the same instant. In this way horizontal cross sectional heart images are displayed on a CRT at a rate of 12 to 50 fields/sec. Since a single phase commutator motor is employed the motor speed can be varied

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Fig 4 Horizontal scan at the level of the aortic valve as in Fig 3. The aortic cusps are closed in diastole. Large left atrium is seen. Right ventricular outflow tract is seen anterior to the aorta. AV = aortic valve. ROT = right ventricular outflow tract.



Fig 5 Transesophageal vertical linear scan through the pulmonary artery in another normal subject. Bifurcation of the pulmonary artery and part of ascending aorta are seen. AO = aorta. PA = pulmonary artery. BI = bifurcation of pulmonary artery.

utilize a transducer of higher frequency increasing resolution of heart images remarkably. Unlike conventional external echocardiograms this system can continuously record heart images from the base to the apex as the transducer is being withdrawn or advanced in the esophagus. Furthermore because of the wider sector angle entire horizontal heart images can be easily observed at the level of the atrioventricular valves. The bifurcation of the pulmonary artery could be readily observed during vertical scanning. However the area above the bifurcation of the pulmonary artery could not be seen because of interference from the trachea. In addition it is easier to obtain M mode esophageal echograms while locating the various cardiac structures utilizing B mode echocardiography.

We have found that the insertion of the transducer for recording heart images through the esophagus is no more difficult than inserting a commercially available gastrofiberscope. The small flexible tube and transducer are easily swallowed and occasional gagging is usually so mild that the examination is hardly interrupted. Although the transducer is moved rapidly there

is no loss of esophageal wall contact nor is esophageal trauma since the oil bag covers the transducer.

Limitations of the described system include (1) fewer scanning planes (horizontal and vertical) available in comparison with conventional surface methods and (2) bubbles which may reduce image resolution occasionally form in the oil bag during linear scanning. However current modifications and developments are devoted to overcoming these limitations.¹¹

In conclusion transesophageal cross-sectional echocardiographic examination can be performed safely and the described system provides high resolution echoes of major cardiac structures in both horizontal and vertical scans. There is a difference in the image quality among each of these. Although this method is in an early stage of development we believe that in the future it will

uated in 31 adult subjects (average age 36.4 years - range 20 to 73 years average height 166.2 cm average body weight 58.7 kilograms). Prior to examination the patients usually received 0.5 mg of atropine sulfate and 10 mg diazepam intramuscularly and 3 g of lidocaine jelly orally. The patients' throats were sprayed with 4% lidocaine liquid. Lidocaine jelly was applied to the oil bag and flexible tube in order to minimize discomfort and the loss of contact with the esophageal wall.

Subjects usually swallowed the oil bag voluntarily and as easily as a commercially available esophageal fibroscope. Oil was then injected into the bag through an external catheter in order to obtain good contact with the esophageal wall.

Insertion of the transducer and transesophageal ultrasound examinations were usually performed with subjects in the left lateral or supine positions.

Results

Following insertion to the 30 to 40 cm level good quality cross sectional heart images were observed in all 31 subjects. All major cardiac structures were observed by withdrawing and advancing the transducer in the esophagus. Complete horizontal heart images were observed from the level of the atrioventricular valves (Fig 3) and the aortic valve (Fig 4). Vertical scanning demonstrated cardiac structures from the level of the aorta to the bifurcation of the pulmonary artery (Fig 5).

Discussion

Since B mode echocardiography has been applied to diagnosis of cardiac disease it has proven useful in anatomical and functional assessment of the heart and several real time imaging systems have been developed. Bom and colleagues and King² have described multi transducer linear scanning systems which display heart images in a rectangular format whereas Griffith and Henry, Eggleton and associates³ and Nishimura and co workers⁴ utilized mechanical sector scanning of a single transducer to produce real time heart images. On the other hand Somer and Von Ramm and Thurstone⁵ developed sector scanning systems to rely on phased array principles without the necessity of mechanical motion. However thoracic configuration excessive chest wall tissue or air containing

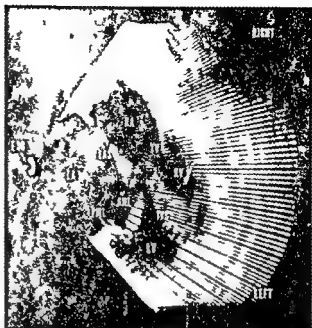


Fig 3 Transesophageal horizontal sector scan during diastole at the level of the mitral and tricuspid valves in a patient with severe mitral stenosis. Tricuspid valve, mitral valve, ventricles and atria are seen. Anterior and posterior mitral leaflets are thickened. ESO = esophagus LA = left atrium RA = right atrium L = left ventricle R = right ventricle IAS = interatrial septum IVS = interventricular septum AVL = anterior mitral leaflet PVL = posterior mitral leaflet TV = tricuspid valve.

lung may often limit the fields of view and resolution. In order to minimize these limitations Frazin and colleagues have recorded M mode echocardiography through the esophagus using a small transducer which patients can swallow. On the other hand Hsuanaga and associates have developed a transesophageal pulsed Doppler echocardiographic system. Although these methods are useful they do not provide two dimensional cardiac images.

We developed a transesophageal cardiac imaging system which can obtain heart images without hindrance from ribs, sternum and lung. Transesophageal echocardiography provides a wider area for study of the heart than that available using a conventional external system. Heart images are observed through esophageal tissue in which ultrasound absorption is very low. Therefore there is little difference in the image quality among various subjects. In clinical examinations one could obtain heart images with very low gain amplitude. Thus one might potentially

Constituents of the human ventricular myocardium Connective tissue hyperplasia accompanying muscular hypertrophy

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The ease with which blood enters and distends the cardiac ventricles during diastole is related to the compliance or stiffness of the ventricular wall. When the wall is stiff a greater energy must be present in the entering blood to produce the same degree of ventricular filling as is produced by blood under lower pressure when the wall has normal compliance. It is the pressure energy of this blood entering the ventricles that when pathologically elevated may lead to the signs and symptoms of congestive heart failure. Thus decreased compliance of the ventricular wall may be a cause of congestive heart failure.

The compliance, stiffness, or tensile stress resisting capacity of the myocardium probably reflects the summation of the mechanical properties of its constituent muscle and interstitial connective tissue. Muscle cells themselves will vary in the deformity or strain produced by an applied stress that is their elasticity depends on their state of contraction. When muscle is relaxed its compliance is high—i.e. it extends

readily under an applied tension.¹ Compliance of the interstitial connective tissue is largely a function of the collagen fibers they contain. Collagen appears to ensheath the tissues in an irregularly coiled or tangled fashion which resists tension only moderately until the fibers are extended whereupon its compliance changes markedly and it becomes highly resistant to further elongation.²

The present study was undertaken to gauge the impression that when hypertrophic cardiac muscle cells develop in response to a pathological process there is concomitant disproportionate increase in the interstitial connective tissues. Composition of the myocardial wall was quantitated histologically in a group of hearts with normal coronary arteries. The values were compared by correlation coefficients with other features of the cases. The study included normal hearts and those with abnormalities that could be expected to increase heart wall thickness both without chamber dilatation. The result was that cardiac muscle cell hypertrophy is accompanied by increase in connective tissue and that the proportion of myocardium and connective tissue remains unchanged.

Materials and methods

Patients listed in the autopsy files of The Hopkins Hospital whose hearts had been examined following postmortem arteriography and in distention³ were reviewed. A case was included in this study if a technically satisfactory

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esophageal cross sectional echocardiography will be useful for cardiac diagnosis in the patient with nondiagnostic transthoracic echoes

Summary

A transesophageal cardiac imaging system is described. This system employs a hand held mechanical sector and linear scanners each having a flexible tube and a small ultrasonic transducer contained within a small oil bag easily swallowed by adults. In the sector scanner a small transducer in the esophagus rotates alternately and horizontal heart images are displayed. In the linear scanner a small transducer in the esophagus moves up and down and vertical heart images are displayed. The system was evaluated in 31 adult subjects. In all subjects stable high quality heart images were observed continuously from base to apex as the transducer was being withdrawn or advanced in the esophagus. In horizontal scans entire heart images were observed at the level of the atrioventricular valves. In vertical scans the bifurcation of the pulmonary artery could be observed clearly. There was little difference in the image quality among subjects.

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Table 1 Muscle cell percentage and nuclear density of the ventricular myocardium*

| Group | Num ber | Age (years) | Heart weight (grams) | Diagnosis of congestive heart failure | Right ventricle | | Inter-ventricular septum | | Left |
|-----------------------|------------|--------------------|----------------------------|---|--|--|--|--|-------------------|
| | | | | | Muscle cell nuclei per grid area | Muscle cell percent of myocardium | Muscle cell nuclei per grid area | Muscle cell percent of myocardium | |
| Normal | 33 | 52 ± 18 (17-87) | 332 ± 57 (220-430) | II | 19 ± 8 (8-38) | 76 ± 8 (57-92) | 19 ± 7 (6-35) | 76 ± 8 (46-90) | 18 ± 8 (9-30) |
| LVH | 28 | 52 ± 18 (17-77) | 636 ± 176 (405-1230) | 12 | 17 ± 4 (10-26) | 75 ± 4 (63-88) | 15 ± 6 (4-26) | 77 ± 7 (62-90) | 13 ± 5 (7-14) |
| RVH | 25 | 52 ± 15 (17-83) | 440 ± 108 (200-700) | 12 | 17 ± 6 (7-28) | 73 ± 7 (58-84) | 19 ± 8 (8-37) | 6 ± 11 (58-94) | 17 ± 6 (10-28) |
| Chronic dilatation | 41 | 50 ± 17 (18-88) | 730 ± 200 (380-1200) | 37 | 15 ± 5 (6-26) | 74 ± 9 (51-90) | 15 ± 6 (8-30) | 73 ± 10 (58-93) | 14 ± 6 (6-37) |
| Total | 127 | 51 ± 17 (17-85) | 552 ± 224 (200-1230) | 61 | 17 ± 6 (6-38) | 74 ± 8 (51-97) | 17 ± 7 (4-37) | 75 ± 9 (46-94) | 16 ± 7 (6-37) |

Mean ± standard deviation (range)
p < 0.01 p < 0.05 (Student's t test) compared to normal

method A grid with 36 intersection points in one 10 power ocular of a binocular microscope was positioned randomly over areas of the myocardial region being studied histologically and the type of tissue each point lay on was determined (Fig 1). Points which fell on empty spaces in the section created as artifacts of preparation were excluded. Such points usually amounted to about 15% of the total. Intersections falling on cardiac muscle cell sarcoplasm or nucleus were called muscle and all other points not on artifactual empty space were considered connective tissue. Between three and six grid settings were evaluated for each area of myocardium using the 25 power objective lens. The grid covered an area of 0.016 mm². Areas to be counted were chosen by scanning the slide under low magnification within this area fields to be counted were randomly selected. The reproducibility of the determinations in serial counts and in blind recounting of slides was excellent rarely greater than 10% difference between counts.

The density of cardiac muscle cell nuclei was determined for each of the three areas of myocardium for which the percent of constituents had been determined. Using the same ocular grid as above the number of cardiac muscle cell nuclei falling within the square were counted for a minimum of five randomly selected fields from right to left ventricular free wall and interventric-

ular septum. Nuclei touching the upper margins of the grid were included though the lower and right margins were excluded. The reproducibility of counts on separate sections and the similarity of values to counts was excellent. The counts expressed as nuclei per grid area (0.016 used for comparison only).

In an effort to study the possible ischemia as the basis for alterations in connective tissue content of the ventricular diameter measurements were made. Major epicardial coronary arteries in studies of these vessels it has been shown cube of a parent vessel diameter approximates the sum of cubes of the branches. Thus in coronary arteries unaffected by sclerotic disease we can construct a theoretical single coronary artery whose diameter cubed equals the sum of diameters of the right and left coronary arteries. In so the angiographic injection of the left coronary was unsatisfactory so this theoretical coronary artery was obtained from the diameters cubed of the right left anterior descending and left circumflex coronaries.

Finally pairwise correlation coefficients (r) were computed for all possible pairs following 12 variables (1) age in years (2) weight in grams (3) body surface area in

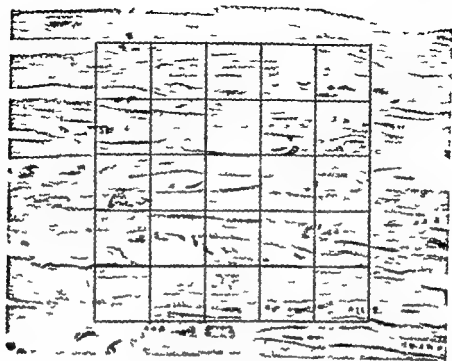


Fig 1 Left ventricular myocardium with superimposed ocular grid used for counting cardiac muscle cell nuclei and determining the myocardial constituents by point counting (Hematoxylin and eosin original magnification $\times 400$)

gram revealed no vascular abnormality and gross examination of multiple transections of the epicardial coronary arteries showed at most only trivial atherosclerosis. Cases with replacement fibrosis or amyloid infiltration that could interfere with the determinations were excluded.

The coronary arteries were injected with a barium gelatin pigment mass at 100 to 150 mm Hg pressure. The heart was then immersed in formalin and fixed in distention at 30 to 40 cm H₂O pressure by intracavitary formalin introduced through cannulae in the atria and great vessels. After fixation stereoscopic radiographs were prepared of the intact heart and the transverse slices into which it was cut. Multiple histological sections of the ventricular myocardium were prepared by routine processing, sectioning and staining which at a minimum included left and right ventricular free wall and interventricular septum taken from transverse sections at the approximate level of the widest diameter of the left ventricle.

Each case was assigned to a disease group based on the results of a previous analysis of the clinical and pathological features. Normal applied to those cases with neither clinical nor pathological

evidence of heart disease. Cases designated LVH were those with left ventricular hypertrophy as the major finding usually secondary to aortic valve stenosis or systemic hypertension.

RVH categorized those cases with predominant right ventricular hypertrophy secondary to pulmonary hypertension as caused by mitral stenosis or pulmonary parenchymal disease. Cases in the Chronic Dilatation group had left ventricular hypertrophy secondary to dilatation as for example with aortic or mitral regurgitation or idiopathic cardiomyopathy. Cases with features of more than one process were assigned to a group according to the predominant or primary abnormality. The determination of the presence of congestive heart failure was made from the available clinical records of diagnoses of the clinicians caring for the patient during life.

The gross and histological features of the ventricular walls were studied for each case. The amount and distribution of interstitial connective tissue was noted for the free wall of right and left ventricle and septum for each heart. The percent of myocardium in each of the three areas which consisted of muscle cell and of interstitial connective tissue was determined by a point count

Table II Correlations (Pearson r) of significant paired variables ($p < 0.01$)^a

| | RV muscle cell nuclei per grid area | RV muscle cell percent of myocardium | IVS muscle cell nuclei per grid area | IVS muscle cell percent of myocardium | LV muscle cell nuclei per grid area | LV muscle cell percent of myocardium |
|--|---|--|--|---|---|--|
| Heart weight | -0.38 | | -0.41 | | -0.43 | |
| RV muscle cell nuclei per grid area | | | 0.46 | | 0.44 | |
| RV muscle cell percent of myocardium | | | | | | 0.1 |
| IVS muscle cell nuclei per grid area | | | | | 0.5 | |
| IVS muscle cell percent of myocardium | | | | | | 0.61 |
| LV muscle cell nuclei per grid area | | | | | | 0.51 |

IVS = interventricular septum; LV = left ventricle; RV = right ventricle.

^aSignificant correlations at the 0.01 level are not displayed. Results show that nuclear density and heart weight are negatively related.

is designed for individual correlations may over estimate the statistical significance of the correlations taken as a whole. It was our intent not to neglect potentially significant linear relationships.

Results

The major characteristics of the 127 patients with normal coronary arteries included in this study are shown by disease groups in Table I. There were 33 normal hearts, 28 hearts with left ventricular hypertrophy, 25 hearts with right ventricular hypertrophy, and 41 hearts with chronic dilatation. The patients were all adults with comparable ages at death. The normal hearts averaged 332 grams while the hearts with right ventricular hypertrophy, left ventricular hypertrophy, and chronic dilatation showed progressively larger abnormal weights. None of the patients with normal hearts, less than half with left and right ventricular hypertrophy, and 90% of cases with chronic dilatation had a clinical history of congestive heart failure.

The normal heart has a nuclear density (Table I) of about 14 per grid area in the interventricular septum and in both ventricular free walls, but the larger diseased hearts, namely those with left ventricular hypertrophy and chronic dilatation, showed significant decreased density of cardiac muscle nuclei (Student's t test) indicating that the cardiac muscle cell increase in size rather than in number. In contrast, determinations of the percentage of muscle cell mass in relation to connective tissue in the heart remains relative

ly constant at 75% of the myocardium in the three segments of the normal human ventricle and is not significantly altered in disease states which enlarge the heart.

Pearson's r coefficient was calculated for all pairs of 12 measurements taken on each heart and is summarized in Table II. Only r values which were significant at the 0.01 level (Student's t test) are displayed. Wall thickness measurements correlated in parallel with heart weight measurements and are not shown here. We found that nuclear density in the three ventricular segments is negatively related to heart weight. Other correlations in this table represent predictable interrelationships of nuclear density of percent muscle to one another between the three different segments of the heart wall. We have explanation for the positive correlation between LV nuclear density and LV percent muscle. In contrast, heart weight is not correlated to percent muscle in all three segments, that is, $p > 0.05$ for all three correlations. We can summarize these correlations by observing that as heart weight increases, myocardial muscle cell nuclear density decreases, showing that muscle hypertrophy occurs with cardiac enlargement. By contrast, the percentage of myocardium consisting of muscle does not change, showing that connective tissue increase is a component of cardiac enlargement.

In some hearts with dilatation and hypertrophy we observed a characteristic increase of connective tissue in the perivascular area shown in Fig. 2. This localized accentuation of connective

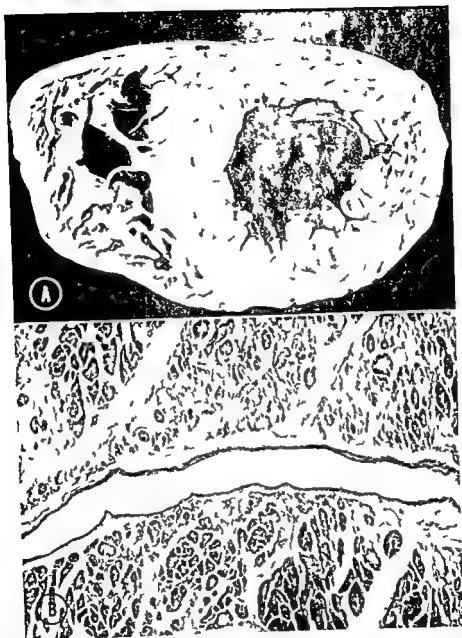


Fig 2 A Transverse section of the ventricles of a markedly enlarged heart with chronic dilatation. The left ventricular free wall myocardium on the right shows numerous striae of connective tissue running between the epicardium and endocardium. The striae are especially prominent in the mid part of the wall. B The striae are found to be an accumulation of interstitial connective tissue around blood vessels on histological examination. (Hematoxylin and eosin original magnification $\times 75$)

right ventricular free wall thickness in cm (5)
 right ventricular free wall nuclear density per grid
 area (6) right ventricular free wall percent mus-
 cle of myocardium (7) interventricular septum
 thickness in cm (8) interventricular septum
 nuclear density per grid area (9) interventricular
 septum percent muscle of myocardium (10) left

ventricular free wall thickness in cm (11) left
 ventricular free wall nuclear density per grid area
 (12) left ventricular free wall percent muscle of
 myocardium. These correlation coefficients were
 used to identify the existence and direction (posi-
 tive or negative correlation) of linear trends in the
 data. It is recognized that this calculation which

shown by the distribution of the fibrosis around the larger intramyocardial arteries (expansive striae) and by correlations which suggest that the large epicardial coronary arteries increase in parallel with cardiac enlargement. Other workers have independently observed an increase in large coronary size with cardiac hypertrophy.

The evidence suggests that cardiac enlargement occurs by muscle cell hypertrophy and by maintenance of a uniform proportion of interstitial connective tissue. The decrease in compliance or increased stiffness associated with congestive heart failure may in some cases result from a simple increase in wall thickness of the myocardium.

Summary

Left sided congestive heart failure may be secondary to decreased left ventricular myocardial compliance in some patients. To investigate the anatomic basis for altered wall stiffness morphometric determinations of muscle cell nuclear density and percent of myocardium consisting of muscle cells were made for right and left ventricular free wall and septum in 127 hearts with normal coronary arteries. The hearts were normal (33 patients) had left ventricular hypertrophy (28 patients) right ventricular hypertrophy (25 patients) or chronic dilatation (41 patients). With cardiac enlargement the average percent of myocardium consisting of muscle did not change from the approximately 75% value characteristic of normal hearts. In contrast muscle cell nuclear density, decreased proportionate to cardiac enlargement demonstrating that muscle cell hypertrophy, not hyperplasia is the basis for weight increase. Some hearts with marked long standing dilatation also had perivascular and interstitial striae of connective tissue differing from replacement fibrosis. An increase in epicardial coronary artery caliber commensurate with increased heart weight suggests that ischemia is not the basis of connective tissue increase. The results show that cardiac muscle cell hypertrophy is accompanied by commensurate increase in interstitial connective tissues. This pattern of myocardial growth with cardiac enlargement may produce increased myocardial stiffness simply as a result of increased wall thickness and may lead to left sided congestive heart failure.

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tive tissue may contribute to increased stiffness of the myocardium in some hearts. That these so called expansive striae are indeed part of the growth process in cardiac enlargement rather than fibrosis secondary to chronic ischemia is suggested first by their location, namely in the distribution of nonatherosclerotic blood vessels which would least likely be ischemic. The lack of an ischemic basis is further supported by correlations of coronary diameter and other variables measured in this study. The diameter of the theoretical coronary is shown in Table III correlated to heart weight and wall thickness and nuclear density of the interventricular septum and left ventricular free wall. These correlation values are all significant at the 0.01 level. The most striking finding is the positive correlation between diameter of the theoretical coronary with heart weight. This suggests that as the heart enlarges total coronary blood flow in these patients grows concurrently to accommodate the needs of the myocardium. The increase of coronary flow with increased interventricular septum and left ventricular free wall thickness likewise suggests that the enlarged hearts in our series developed compensatory blood flow. As previously demonstrated a decrease in the nuclear density parallels cardiac hypertrophy and likewise correlates with increased coronary flow. All these correlations support the concept that the enlarged hearts in this series stimulate the necessary blood flow and do not develop increased connective tissue on the basis of ischemia.

Discussion

Many patients with enlarged ventricles develop congestive heart failure. One explanation for this congestive failure may be a decreased compliance of the ventricular myocardium. In this study we examined 127 hearts from autopsied patients with normal coronary arteries and no destructive or infiltrative myocardial lesions. About half the patients in the study carried a clinical diagnosis of congestive heart failure and had enlarged hearts at autopsy. With cardiac enlargement cardiac muscle cells were found to increase in size while the proportion of connective tissue remained unchanged. The increase in weight of the adult heart predominantly by hypertrophy has been observed by other workers both experimentally in dogs and in autopsy studies of humans. In infants and in neonatal dogs by contrast

Table III Variables significantly correlated (Pearson's r) to the diameter of the theoretical coronary artery ($p < 0.01$)^a

| Variable | r |
|--------------------------------------|-------|
| Heart weight (grams) | 0.57 |
| IVS wall thickness (cm) | 0.33 |
| IVS muscle cell nuclei per grid area | -0.31 |
| LV wall thickness (cm) | 0.29 |
| LV muscle cell nuclei per grid area | -0.30 |

IVS = interventricular septum; LV = left ventricle.

^aNon-significant correlations at the 0.01 level are not displayed. Results show that coronary lumen size increases with increased heart weight.

increase in heart weight occurs by hyperplasia. Experimental evidence relating the amount of myocardial collagen to the degree of ventricular enlargement has been equivocal. In hypertrophy caused by valvular disease the content of myocardial collagen increases,¹ whereas in thyroxine induced hypertrophy the total collagen decreases.² Thus a mechanically induced ventricular hypertrophy may decrease ventricular wall hypertrophy by increasing total collagen, while a metabolically mediated collagen loss may allow the ventricles to dilate because of increased compliance. The human hearts in the present series appear to be more closely akin to the mechanical interpretation.

Similar quantitative studies of the myocardial constituents were performed on autopsied patients with chronic mitral incompetence and hypertensive heart disease.⁴ Myocardial fiber diameter and proportion of interstitial tissue were obtained from computer analysis of enhanced photographs. These workers noted a somewhat higher proportion of interstitial tissue than we did (32% against our 25%) but this may be due to the avoidance in our method of large vascular spaces and artifactual tissue spaces. They also found a more than proportionate increase in patients with severe mitral incompetence which may correspond to our qualitative observations of expansive striae in chronically dilated hearts. These workers found a diffuse hypertrophy in both groups of diseased hearts similar to our observations.

It could be argued that the increase in perivascular connective tissue seen in some enlarged hearts in this study is mostly ischemic in nature with the hypertrophied myocardium outrunning its blood supply. That this is not the case is

SEPTAL FIBROSIS (LEFT SEPTAL BLOCK)

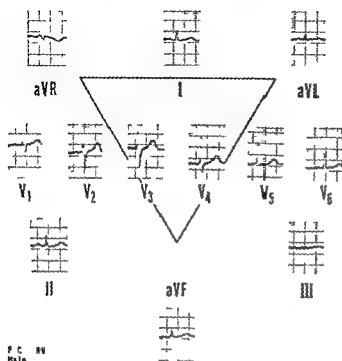


Fig 1 The ECG of a 49 year old male patient with a six month history of angina pectoris. The treadmill test was positive. The myocardial scan showed absent septum perfusion and coronary angiography revealed occlusion (100%) of the LAD at its origin and 90% narrowing of the principal diagonal at its origin.

grams electrocardiograms and clinical records of 274 patients studied at Loma Linda University Medical Center Loma Linda California over a four year interval were analyzed. The series with obstructive coronary artery disease consisted of 178 patients with chest pain most of whom had greater than 70% estimated cross sectional obstruction in one or more coronary arteries. The ECGs of 96 patients without angiographic evidence of obstructive coronary artery disease were reviewed for ECG changes of the syndrome.

A 12 lead electrocardiogram recorded on a high sensitivity paper was examined by two observers for absence of Q waves in Leads I, aVL, V₁, V₂ and V₃ and evidence of myocardial ischemia and/or infarction. Records showing absence of Q waves with clockwise rotation on the long axis, right or left bundle branch block and bilateral bundle branch block were excluded. Some patients were exercise stressed on a computer controlled treadmill with three minute work

loads beginning with 1.7 MPH at a 5% grade, increasing to 1.7 MPH at a 10% grade, 2.5 MPH at a 12% grade, 3.4 MPH at a 14% grade and 4.3 MPH at a 16% grade. The exercise was continued up to the point of fatigue, chest pain or dyspnea. Heart rate, arterial pressure, ECG morphology and symptoms were continuously monitored throughout. Exercise stress testing was not done on patients with recent acute myocardial infarction.

Selective coronary arteriography was carried out by the Judkins technique. 'Ventriculography' was performed and recorded in the RAO 30 degree and LAO 20 degree projections in biplane cineradiography. The coronary arteries were imaged in the AP, RAO 20 degree, LAO 20 degree lateral and LAO cranio-caudal projections using 35 mm cineradiography and 100 mm photofluorography.

The extent of artery narrowing was estimated from the multiprojection views of the coronary arteries. The narrowing was expressed as a percent cross sectional obstruction and the agreement among different arteriographers of the extent of narrowing was remarkably close.

In analyzing the topography of obstructive coronary artery disease, the major coronary arteries were divided into proximal, mid and distal regions. For the left anterior descending artery, the region from the origin to the take-off of the first septal perforator was designated proximal; the region extending from the first septal perforator to the take-off of the second anterior branch was designated mid; the region extending from the second anterior branch to the take-off of the third anterior branch was designated distal. The proximal region of the circumflex artery extended from its origin to the take-off of the obtuse marginal artery; the mid region extended from the obtuse marginal to the posterior lateral left ventricular artery or posterior descending artery; and the distal segment extended to the remaining posterior continuation(s) of the circumflex. The proximal region of the right coronary artery extends from the take-off to the acute marginal artery; the mid region extends from the acute marginal to the posterior descending artery; and the distal region extends as the distal continuation of the artery.

In some patients following coronary arteriography, 99m technetium microspheres (25 to 100 μ Ci) were injected into the left coronary artery and 131 I macroaggregated albumin (131 to 100 μ Ci) were injected into the right coronary artery. Other patients received differing amounts of

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Witham surveyed 200 patients with classical angina pectoris and identified 40 patients with

As part of a continuing effort to refine the clinical assessment of coronary pathology we examined for relationships between obstructive coronary artery disease myocardial perfusion and the ECG syndrome of septal fibrosis in a series of patients studied with coronary arteriography and myocardial scintigraphy. It was learned that patients with angina pectoris and the ECG syndrome of septal fibrosis have a higher incidence and a more extensive narrowing of the proximal LAD by obstructive coronary artery disease and a greater ventricular septal hypoperfusion than patients without the syndrome. The fact that the ECG syndrome of septal fibrosis occurs in only 4% of age matched patients with angiographically determined coronary arteries free of obstructive disease strongly supports the usefulness of this ECG finding in identifying a subset of angina pectoris patients with a high probability of proximal LAD disease and left ventricular hypoperfusion.

The coronary arteriograms left ventricular cineangiograms myocardial perfusion scinti

†This investigation is dedicated to Dr. M. I. P. J. d'Amico, pioneer in quality control in stenography.

Table III Atheromatous disease of the proximal left anterior descending artery and the ECG syndrome of septal fibrosis

| Groups | Number | Frequency of $\geq 70\%$ narrowing (%) | % narrowing |
|--------|--------|--|----------------------|
| A + B | 41 | 68 | 74 \pm 6 |
| C | 48 | 45 | 54 \pm 4 |
| p | | < 0.001† | A + B vs C — < 0.01‡ |

Mean \pm standard error

Statistical probability † Student's t test ‡ Chi square test

patients in the three groups patients with the ECG syndrome of septal fibrosis (Groups A and B) had a mean narrowing of 74% in contrast to 54% for patients without the syndrome (Group C)

One hundred and forty six patients had myocardial scintigraphy 62 with and 84 without the ECG syndrome of septal fibrosis (Table IV). Nearly 60% of the patients with the ECG syndrome of septal fibrosis (Groups A and B) have abnormal perfusion of the ventricular septum as opposed to 23% of the patients without septal fibrosis (Group C) a highly significant difference ($p < 0.001$). The percentage of patients with abnormal perfusion of the remaining left ventricle may also be greater in patients with (Groups A and B) than in patients without the ECG syndrome of septal fibrosis (Group C) ($p < 0.05$).

As judged from the findings presented in Tables III and IV no differences in the proximal LAD pathology or in the extent of left ventricular hypoperfusion are seen in comparisons of Groups A and B patients.

To determine the incidence of the ECG syndrome of septal fibrosis in individuals without angiographic evidence of obstructive coronary artery disease the ECGs of 96 randomly selected records from the Radiology Museum at Loma Linda were reviewed. The patients presented with atypical angina like chest pain. Out of these 96 patients only four had the ECG changes of septal fibrosis.

Discussion

Sodi Pallares and colleagues in a definitive study on the depolarization activation of the ventricular septum in dogs reported the orientation of the initial QRS vector as proceeding from the left side (midway between the anterior and posterior edges of the septum at the juncture of the lower two thirds with the upper one third of

the septal surface) towards the trabecular and the apex of the right ventricle. The L muscle mass activated on the left side of the septum generates a voltage field that in-creases Q wave in leads I, aVL, V₁, V₂, and V₃. A small initial septal depolarization from left to right occurs for the human heart and an absence of Q wave in Leads I, aVL, V₁, V₂, and V₃ reflect according to Goldman's a parallel orientation of the ventricular septum with respect to the recording electrodes. Scarring of the middle third of the ventricular septum, left bundle branch block, preexcitation syndromes where the initial depolarization proceed anteriorly from right to left.

A positive correlation between the severity of obstructive lesions in the proximal LAD and the ECG syndrome of septal fibrosis (Table II) reflects the key role of the LAD in transporting blood to the ventricular septum. The region where the left bundle branch ramifies and the initial ventricular septal depolarization commences is supplied by proximally located septal penetrating branches from the LAD. Atheromatous lesions proximal to the first perforating branch causing a significant (< 50%) luminal narrowing would therefore reduce the blood flow to the ventricular septum and cause ischemic injury, loss of myocardium and ultimately fibrosis in the region of the penetrating His-Purkinje bundle responsible for the initial septal depolarization. Group C patients on the other hand with a lower incidence and extent of critical proximal LAD narrowing would have reduced incidence of septal fibrosis.

Finding approximately 60% of patients with the ECG syndrome of septal fibrosis having abnormal ventricular septal myocardial scintigrams (Table IV) represents a positive correlation between the near 75% narrowing of proximally located obstructive LAD lesion (Table III) and reduced blood flow to the ventricular septum. This 6% value contrasts sharply with the 23% value for Group C patients without the ECG syndrome of septal fibrosis and where the extent of atheromatous narrowing of the proximal LAD is only 54% (Table III).

A more extensive coronary pathology and left ventricular hypoperfusion might have been predicted for Group II as compared to Group I patients with the ECG syndrome of septal fibrosis. The fact that the two groups are indistinguishable by the various examinations included in this study points up the serious implication of

Table I Patients with and without the ECG syndrome of septal fibrosis

| Groups | Number | Age | Sex | | Duration of angina (months) | Stress testing | | |
|--------|--------|----------------|-----|----|-----------------------------|----------------|----------|-----|
| | | | M | F | | Negative | Positive | % |
| A | 30 | 56.5 ± 1.45 | 26 | 4 | 28.83 ± 7.52 | 2 | 28 | 91 |
| B | 35 | 59.5 ± 1.51 | 29 | 6 | 23.14 ± 6.4 | 0 | 14 | 100 |
| C | 113 | 57.0 ± 0.77 | 95 | 18 | 36.57 ± 4.50 | 20 | 43 | 63 |
| D | 96 | 49.5 ± 1.62 | 52 | 44 | ~ | ~ | ~ | ~ |

Mean and \pm standard error

technetium microspheres injected down the two coronary arteries. At the end of the injections the patient was taken to the Nuclear Medicine Section and multiple views with an Anger camera were integrated in a data acquisition storage processing and display system using a computer controlled color coded display system developed by Adams and associates*. The images were photographed separately as a series of 10 color coded isocount contours in spectral sequence. The channel with the maximum counts was arbitrarily assigned the color red and each 10% change in counts resulted in a different color. The scintigrams of the left and right coronary circulations appeared separately in combination and color. Heparin (2 500 to 5 000 units) was given intravenously at the beginning of the study and was reversed by protamine intravenously at the end of the procedure.

Results

The patients were divided into four groups. Groups A, B and C were patients with angina pectoris—Group A patients with the ECG syndrome of septal fibrosis (Fig. 1). Group B patients with the ECG syndrome of septal fibrosis and ECG changes of myocardial ischemia and/or infarction. Group C patients with ECG changes of myocardial ischemia and/or infarction but without septal fibrosis. Group D was composed of patients with chest pain but normal coronary arteries as shown by coronary arteriography. Thirty patients were in Group A, 35 in Group B, 113 in Group C and 96 in Group D (Table I).

The age and sex distribution for Groups A, B and C patients with angina pectoris is similar but a high percentage of females occurs in Group D patients. The duration of angina pectoris is similar in patient Groups A, B and C. Of the 38

Table II Obstructive ($\geq 70\%$ narrowing) coronary lesions and the ECG syndrome of septal fibrosis

| Groups (no.) | Artery involvement | | | | | | |
|--------------|--------------------|-------|----|------------|-------|------------|----|
| | LAD | | | | CIRCX | | |
| | LAD | CIRCX | RC | CIRCX + RC | CIRCX | CIRCX + RC | RC |
| A (30) | | 8 | 2 | 10 | 0 | 1 | 2 |
| B (35) | 4 | 5 | 5 | 1 | 2 | 1 | 1 |
| C (105) | 15 | 22 | | 45 | 6 | 3 | 7 |

Abbreviations: no = number of patients; LAD = left anterior descending artery; CIRCX = circumflex artery; RC = right coronary artery.

exercise stressed patients with septal fibrosis (Groups A and B) 36 (96%) had positive responses as compared to 43 out of 68 (63%) for Group C patients.

The number of arteries with a greater than 70% estimated cross sectional obstruction in Groups A, B and C patients is given in Table II. No differences are seen in the number of obstructed arteries relative to the number of patients in the three groups.

Differences in the pathology of obstructive coronary arteries between the groups with (A and B) and without (C) septal fibrosis are seen in the frequency and severity of proximally located disease (Table III). Forty four (44) out of 65 patients (68%) with the ECG syndrome of septal fibrosis (Groups A and B) had obstructive lesions ($\geq 70\%$) in the proximal LAD as compared to 48 out of 105 patients (45%) without the ECG syndrome—a difference that is highly significant ($p < 0.001$). Considering the estimated atherosclerotic narrowing of the proximal LAD for all of the

Long-term benefit of dobutamine in patients with congestive cardiomyopathy

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Dobutamine is a new synthetic catecholamine systematically formulated by Tuttle and Mills.¹ Animal experiments demonstrated that this compound significantly increased ventricular contractility and cardiac output in a dose range which had little to no effect on heart rate and systemic blood pressure.^{2,3} Short and long term infusions of dobutamine in patients with cardiac failure also improved ventricular performance and increased cardiac output while decreasing left ventricular filling pressure and systemic vascular resistance. These beneficial effects were achieved without a significant increase in afterload or heart rate.⁴ This laboratory previously reported that the mean cardiac index and left ventricular function parameters (echocardiograms and systolic time intervals) remained unimproved above baseline values 30 minutes after the discontinuation of a 72 hour dobutamine infusion (in patients with congestive cardiomyopathy and severe car-

diac failure) symptomatic improvement persisted up to one week post infusion in 68% of patients. The purpose of this study is to determine whether prolonged infusion of dobutamine results in persistent symptomatic and objective improvement of cardiovascular function in patients with low output cardiac failure.

Methods

Patient population The 38 patients selected for the study had symptoms of severe left heart failure. There were 29 men and nine women; age range was 17 to 73 years, the mean age was 51.2 years. The diagnosis of congestive cardiomyopathy (CCM) was made by history, physical examination and cardiac catheterization. Patients who had a greater than 50% occlusion of a coronary artery by angiography were excluded from the study. Also excluded were patients who had consumed more than one drink of alcohol per day for the three months prior to study. The etiology of the heart disease was commonly idiopathic (20 of 38, 53%) but other factors were also important (Table 1). Frequently two factors such as alcohol and hypertension may have contributed. The protocol was approved by the Human Research Committee.

This group of 38 patients can be further characterized by their symptoms. Physical and electrocardiograms and hemodynamic data. Symptoms at time of study included dyspnea (37 of 38, 100%), peripheral edema (20 of 38, 53%), atypical chest pain (18 of 38, 47%), easy fatigability (10 of 38, 26%), palpitations (nine of 38, 24%) and abdominal swelling (nine of 38, 24%). The most prominent physical findings were

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Table IV Myocardial scintigrams and the ECG syndrome of septal fibrosis

| Groups (no.) | Septum | | | | Left ventricle | | | |
|-----------------|-----------------------|----|----------|----|----------------------|----|----------|----|
| | Normal | | Abnormal | | Normal | | Abnormal | |
| | No | % | No | % | No | % | No | % |
| A (28) | 13 | 46 | 15 | 54 | 10 | 35 | 18 | 63 |
| B (34) | 12 | 35 | 22 | 65 | 8 | 23 | 26 | 77 |
| C (84) | 64 | 77 | 20 | 23 | 41 | 48 | 43 | 50 |
| p | A + B vs. C - < 0.001 | | | | A + B vs. C - < 0.05 | | | |

No = number of patients

Statistical probability Chi sq are test.

what might be considered a minor ECG abnormality the loss of Q wave from the initial depolarization through the ventricular septum

It may be more than coincidence that the 23% of patients without the ECG syndromes of septal fibrosis had abnormal septal scintigrams while Burch and De Pasquale² found a 20% incidence of histologically proven septal fibrosis in the 1184 hearts with previous ECG evidence of normal septal depolarization. A most likely explanation for this similarity is that septal fibrosis or infarctions in regions remote from the initial depolarization pathway do not affect the Q wave inscription in the ECG leads subtending the ventricular septum.

The 96% positive exercise stress response the significantly higher incidence of proximally located obstructive lesions of the LAD (Table III) and the higher percentage of abnormal ventricular septal and left ventricular myocardial scintigrams (Table IV) coupled with the infrequency of the ECG syndrome of septal fibrosis in patients with nonobstructive coronary artery disease (4%) when viewed together provide compelling evidence that the ECG syndrome of septal fibrosis is a useful clue for identifying a subset of angina pectoris patients with advanced coronary artery disease of the proximal LAD and diffuse left ventricular hypoperfusion.

Summary

Coronary artery disease (CAD) and myocardial perfusion were assessed by arteriograms and scintigrams (Technetium 99 microspheres alone or combined with Iodine 131 albumin macroaggregates) in 178 angina pectoris patients with and without the electrocardiographic (ECG) syndrome of septal fibrosis and with $\geq 70\%$ obstruction in one or more coronary arteries. The ECGs of 96 patients without angiographic evidence of

obstructive CAD were also examined for the ECG syndrome of septal fibrosis. Patients with the ECG syndrome of septal fibrosis have a significantly higher incidence of positive exercise stress test of $\geq 70\%$ narrowing of the proximal left anterior descending (LAD) artery of severe proximal LAD disease and of more extensive left ventricular hypoperfusion than patients without the ECG syndrome. The fact that only 4% of patients without obstructive CAD have the ECG syndrome of septal fibrosis indicates the usefulness of the syndrome in identifying a subset of angina pectoris patients with advanced CAD of the proximal LAD and diffuse left ventricular hypoperfusion.

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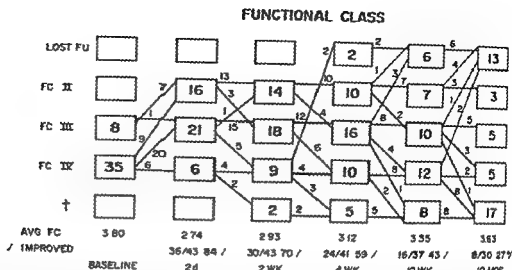


Fig 1 This graph details the number of patients in each functional class (FC) at each time period from baseline to 10 months after completion of the dobutamine infusion. If we could not contact a patient, he was considered lost to follow up (Lost FU). Those who died (†) were considered to be in FC IV for average FC determinations; those lost to follow up were not included in average functional class determinations. Only those patients in a higher functional class compared to their baseline were considered improved for the percent improved of this graph.

functional class determination via telephone interviews

Results

The 38 patients received a total of 43 three day infusions of dobutamine; five patients received the drug twice. Every patient improved his cardiac function during the infusion as measured by the $\% \Delta D$ and the PEP/LVET. The average increase of $\% \Delta D$ was $68\% \pm 0.7$ ($\bar{x} \pm SEM$, $p < 0.001$) and the average decrease of the PEP/LVET was 0.16 ± 0.3 ($\bar{x} \pm SEM$, $p < 0.001$). Most patients continued to have subjective and objective evidence of improved left ventricular function after discontinuation of the drug.

The improvement of functional class (FC) after dobutamine is shown in Fig 1. The average FC of all patients prior to dobutamine was 3.8. Two days after completion of dobutamine the average FC was 2.7 and at two weeks it was 2.9. Even at four and ten weeks the FC was 3.1 and 3.4. By 10 months however the average FC was 3.6. The number of patients improved decreased from 83% at two days and 70% at two weeks to just 27% at 10 months.

Results of serial systolic time intervals are shown in Fig 2. The data were best organized over four time periods. If a patient had more than one measurement during this interval the data were averaged. Those patients studied maintained a significant ($p < 0.001$) decrease of the

PEP/LVET over pre drug control at all four periods. Similarly the echocardiographic $\% \Delta D$ shown in Fig 3. This shows a significant ($p < 0.05$) improvement at 23 days and impressive changes at 43 weeks and 99% at 104 months ($p < 0.01$).

Fig 4 details the results of the systolic intervals after discontinuation of dobutamine; the time when measurements were taken change from baseline is shown. Improvement considered significant if there was a one standard deviation (-0.04) change. This standard deviation was established by sequential study of patients with chronic myocardial disease. Patients who died of congestive heart failure considered as having deteriorated in their condition tests. However those who died of arrhythmias, embolus or other causes were not entered in this table. Those test results that indicate a change of -0.04 are connected by a solid line to indicate improvement. A lesser change or a rise in the PEP/LVET is shown by a broken line. At the time period seven days after dobutamine 67% of 30 had an improved PEP/LVET. At 10 months 52% (12 of 23) were better and even at 10 months 31% (five of 16) had evidence of improved left ventricular function.

The change of $\% \Delta D$ from baseline is shown in Fig 5. Improvement was considered significant if there was a 2% rise in this measurement. The rise was considered significant because in a

allop rhythm in all 38 patients 92% (35 of 38) and a left ventricular protodiastolic gallop and 4% (28 of 38) had a left ventricular presystolic gallop. Right ventricular protodiastolic (13 of 38 4%) and presystolic (11 of 38 32%) gallop sounds were also noted. The murmur of mitral regurgitation was present in 61% (23 of 38) and tricuspid regurgitation was observed in 16% (six of 38) of the patients. The electrocardiograms often showed conduction disease. There were 11 patients (11 of 38 29%) with complete left bundle branch block and 16 (16 of 38 42%) with left intraventricular conduction delay. Also 11 patients (11 of 38 29%) had a left axis deviation and three (three of 38 8%) had a right bundle branch block. Arrhythmias were frequently recorded. Seven patients (seven of 38 18%) had atrial fibrillation and twelve (12 of 38 32%) had frequent premature atrial or ventricular contractions. Findings at catheterization were consistent with severe left heart failure. The angiographic ejection fraction ranged from 0.09 to 0.42 with a mean of 0.25 ± 0.02 ($\bar{x} \pm \text{SEM}$) and the cardiac index ranged from 1.5 to 2.9 liters/min/M ($\bar{x} = 2.0 \pm 0.1$). The pulmonary wedge pressure averaged 23.4 mm Hg ($\bar{x} = 23.4 \pm 1.9$).

Infusion period and studies. Written informed consent was obtained from each patient. Dobutamine was delivered intravenously with a calibrated Harvard pump for 72 hours. Dobutamine was started at 2.5 mcg/kg/minute and was increased every 30 minutes in 2.5 mcg/kg/minute dose increments up to a maximal dose of 15 mcg/kg/minute. The maintenance dose for each patient was determined on the basis of data derived from the dose response phase and had to meet the following criteria: heart rate increase of $< 120\%$ of control; systolic blood pressure $< 120\%$ of control; pulmonary capillary wedge pressure $< 140\%$ of control; and premature ventricular contraction of $< 12/\text{minute}$. After six hours of the maintenance dose and daily thereafter the dose was reevaluated for each patient and was increased or decreased based on the criteria noted above.

The electrocardiogram was monitored continuously over the 24 hours prior to the infusion period and continually during the infusion. An echocardiogram and systolic time interval determinations were performed 30 minutes before the infusion began daily during the infusion period and at intervals as discussed below. Systolic time

Table 1 Contributing factors to heart failure (38 patients)

| | | |
|------------------------|-------------|-----|
| Idiopathic | 0 patients | 5% |
| Alcohol | 17 patients | 45% |
| Hypertension | 10 patients | 26% |
| Possible viral disease | 4 patients | 11% |
| Peripartum | 3 patients | 8% |
| Diabetes | 3 patients | 5% |
| Amylodosis | 2 patients | 5% |

intervals were obtained with an Electronics for Medicine VR6 or with a Smith Kline French Echoline 20 unit utilizing the specifications previously outlined.⁶ The PEP/LVET was used as the measure of left ventricular performance. Echocardiograms were performed with a Unirad series C echoscope and an Electronics for Medicine VR6 recorder or an Irex echoscope with the SKF Echoline 20 recorder. The %SD was used as the echocardiographic determinant of left ventricular function and was derived from the formula

$$\%SD = \frac{\text{end diastolic diameter} - \text{end systolic diameter}}{\text{end diastolic diameter}} \times 100$$

The left ventricular free wall thickness and end diastolic diameter were measured at end-diastole prior to dobutamine infusion.

Follow up information. Patients were contacted and were encouraged to return to the medical center for an interview, physical examination and non invasive measurement of left ventricular function. The functional class determinations were made by two of the investigators (DVU and CVL). Patients were considered lost to follow up for functional class determination if we were unable to contact them or if they were started on additional drug therapy. Initiation of additional drug therapy was not necessarily a sign of dobutamine failure because many patients were placed in other studies after several months. Patients who died were considered to be in the unimproved functional category despite the fact that several patients had objective and subjective signs of improvement but died of an embolus or a dysrhythmia. Digitalis and diuretics were maintained at the same dosage level throughout the study. Vasodilators were not prescribed. Patients who were unable to travel were excluded from the non invasive measurement portion of this study but were included in the

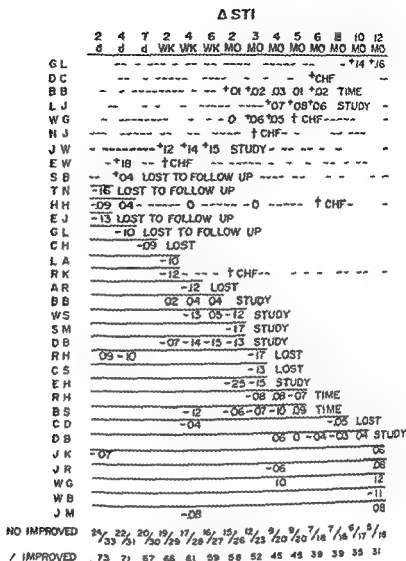


Fig. 4 The change of each patient's PEP/LVET from baseline are shown. Those who died (†) and the cause of death (CHF = congestive heart failure) are noted. The study was completed while some patients were under observation (Time), some patients were placed on another study (Study), and some could not travel to the medical center for examination (Lost = lost to follow up). Those who had an improvement of less than -0.04 or who had a worsening of the ratio or who died are noted by a dashed line linking their initials to their data. Those patients who had an improvement of greater than -0.04 of the PEP/LVET have a solid line linking their initials and running above their data. Those who died or did not improve were considered to be unimproved for all 10 months of the study. Those who improved the PEP/LVET were considered to be improved only for the time of observation. The percent improved at each time period after dobutamine is shown at the bottom of the graph.

diagrams 22 (58%) had a decrease of their left ventricular diameter.

The average survival of these patients from the onset of symptoms was approximately nine years and is illustrated in Fig. 11. No patient has survived more than 20 years from the onset of symptoms. The cause of death in the 17 patients who died during the time of the study was pulmonary embolus (six of 17, 35%), intractable left heart failure (six of 17, 35%), ventricular

arrhythmias (four of 17, 23%), and sepsis (four of 17, 6%).

Discussion

Therapy of congestive cardiomyopathy has traditionally been digitalis and diuretics. There was a wave of popularity for extended bed rest in the 1960s and the early 1970s. "This treatment decreased heart size in those with alcoholic or idiopathic cardiomyopathy."

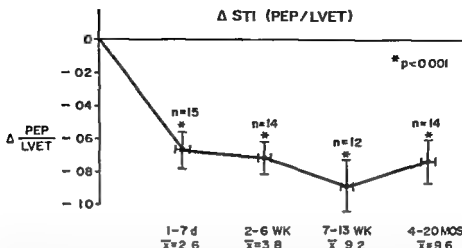


Fig 2 The change of the PEP/LVET of the systolic time intervals from baseline is shown at four time periods after dobutamine infusion. The number of patients measured at each period is shown. Some patients had two or more measurements made during a time period and these were averaged. Brackets represent the standard error of the mean.

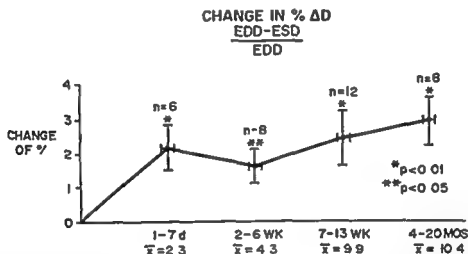


Fig 3 The change of the echocardiographic ΔD from baseline at four time periods after dobutamine infusion is shown. The number of patients measured during each period is shown. Some patients had two or more measurements during a time period; these values were averaged. The brackets represent the standard error of the mean.

of 15 patients with stable heart failure the one standard deviation of serial ΔD measurements of the echocardiograms was 1.7%. At one week after discontinuation of dobutamine 60% (18 of 30) had an unimproved ΔD . At two and six weeks 55% (16 of 29) and 50% (14 of 28) were still unimproved. At three, six, and 12 months 48% (13 of 27), 42% (10 of 24), and 22% (four of 18) had a ΔD at least 2% better than control.

The left ventricular wall thickness (LVWT) had some prognostic implications. Those patients who had symptomatic improvement had a thicker

left ventricular free wall (corrected for body surface area) $0.59 \text{ cm/M}^2 \pm 0.03$ ($\bar{x} \pm \text{SEM}$) compared to those who did not improve $0.53 \text{ cm/M}^2 \pm 0.04$. Also only 24% (seven of 29) of those who improved had LVWT less than 0.5 cm/M^2 while 56% (five of nine) of those who did not improve had LVWT less than 0.5 cm/M^2 .

The left ventricular end diastolic diameter decreased slightly from an average pre dobutamine value of $6.58 \pm 0.17 \text{ cm}$ ($\bar{x} \pm \text{SEM}$) to a post dobutamine diameter of 6.45 ± 0.14 ($p < 0.05$). Of the 38 patients who had echocar

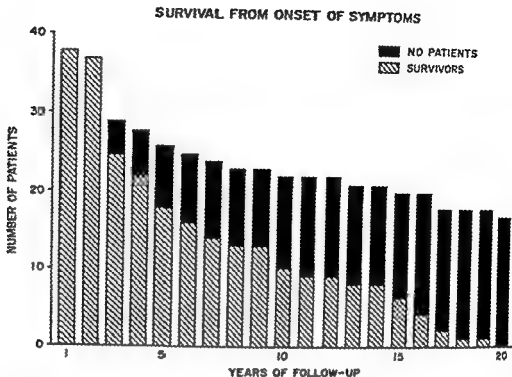


Fig 6 This graph demonstrates the survival of our 39 patients from the onset of symptoms. The total number of patients is shown by the height of the bars. Those who are still living at each year are illustrated by the cross hatched portion of the bars while those who have died are shown by the solid portions of the bars.

ogy of the particular patient's heart failure before institution of veno or arteriolar dilators.^{1,20} Caution has been urged in the use of nitrates, hydralazine, and prazosin because of both pharmacologic effects and adverse reactions.²⁰ Because of the potential adverse effects of vasodilators and because not all patients improve with vasodilators, consideration should be given to inotropic agents in the treatment of congestive cardiomyopathy.

This study demonstrated that dobutamine induced an improvement of myocardial function both during the three day infusion and in the follow up period. Most of the patients (84%) had symptomatic improvement two days after infusion. 59% continued to feel better at four weeks and 43% continued to feel better at ten weeks (Fig 1). This improvement was documented by non invasive testing. The PEP/LEVT was significantly improved at three days, four and 10 weeks and at 10 months (Fig 2). The echocardiographic ΔD was similarly significantly improved (Fig 3) in those patients whom we could recall for testing. The number of patients improved at each time period is similar for the two tests with approximately 50% still maintaining improve-

ment at three months. Even at six months, 38% and 42% were improved by PEP/LEVT and ΔD .

There was a small ($14 \text{ mm} \pm 0.7$ ($p < 0.05$)) but significant decrease of end diastolic diameter by echocardiogram after the three day infusion. The patients who had a functional class improvement usually had a thicker left ventricular wall (greater than 0.5 cm/M^2) than those who did not respond. This is consistent with Hamer's study.² He found that the patients with thick left ventricular walls had a better prognosis than those with a thin wall.

The mechanism of the prolonged improvement of COCM patients after a three day infusion of dobutamine is not understood. The downward spiral of a decreasing cardiac output increasing peripheral vasoconstriction and fluid retention is corrected during the infusion period. The reversal of this spiral may enable the ventricle to assume a new level of function with a reduced peripheral resistance. Another possible mechanism for prolonged functional improvement may be related to increased coronary artery flow. Dobutamine not only increases cardiac output but also by stimulation of its beta-1 action dilates coronary arteries.

ECHO % Δ D CHANGE FROM BASELINE

| | 2 | 4 | 7 | 2 | 3 | 4 | 6 | 2 | 3 | 4 | 5 | 8 | 10 | 12 |
|----|---|---|---|----|----|----|----|----|----|----|----|----|----|-------------|
| | d | d | d | WK | WK | WK | WK | MO | MO | MO | MO | MO | MO | MO |
| DC | | | | | | | | | | | | | | |
| WG | | | | | | | | | | | | | | †CHF |
| EH | | | | | | | | | | | | | | †CHF |
| NJ | | | | | | | | | | | | | | †CHF |
| RK | | | | | | | | | | | | | | †CHF |
| SM | | | | | | | | | | | | | | -2- STUDY |
| DB | | | | | | | | | | | | | | +1-+1 STUDY |
| JB | | | | | | | | | | | | | | |
| JW | | | | | | | | | | | | | | |
| NJ | | | | | | | | | | | | | | |
| EJ | | | | | | | | | | | | | | |
| GL | | | | | | | | | | | | | | 5 |
| RH | | | | | | | | | | | | | | |
| SB | | | | | | | | | | | | | | |
| CH | | | | | | | | | | | | | | |
| HK | | | | | | | | | | | | | | †CHF |
| BB | | | | | | | | | | | | | | |
| WS | | | | | | | | | | | | | | |
| CS | | | | | | | | | | | | | | |
| RH | | | | | | | | | | | | | | |
| LJ | | | | | | | | | | | | | | |
| EH | | | | | | | | | | | | | | |
| TN | | | | | | | | | | | | | | |
| BS | | | | | | | | | | | | | | |
| DB | | | | | | | | | | | | | | |
| BB | | | | | | | | | | | | | | |
| WG | | | | | | | | | | | | | | |
| JM | | | | | | | | | | | | | | |
| WB | | | | | | | | | | | | | | |
| HC | | | | | | | | | | | | | | |
| JK | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | |
|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|
| NO IMPROVED | 22/ | 21/ | 18/ | 16/ | 16/ | 15/ | 14/ | 14/ | 13/ | 12/ | 12/ | 10/ | 7/ | 5/ | 4/ |
| | 31 | 30 | 30 | 29 | 29 | 29 | 28 | 28 | 27 | 26 | 26 | 24 | 21 | 19 | 18 |
| / IMPROVED | 71 | 70 | 60 | 55 | 55 | 55 | 50 | 50 | 48 | 46 | 46 | 42 | 33 | 26 | 22 |

Fig 1 The change of each patient's echocardiographic Δ D from baseline is illustrated. Those who died (*) and the cause of death (CHF = congestive heart failure) are noted. The study was completed while some patients were under observation (Time) some patients were placed on another study (Study) and some could not come to the medical center for further examination (lost to FU). The patient's initials are connected to their data by a dashed line if the improvement was less than 2% or if the patient died (CHF). The initials are linked by a solid line that runs over the data if there was a 2% or greater improvement of the Δ D. The percent improved at each time period is shown at the bottom of the graph.

and improvement was maintained for months in some of these patients'. This treatment has not had a great deal of popularity in recent years however because of the practical problems of maintaining strict bed rest. Also some investigators have found that in certain types of heart disease such as peripartur cardiomyopathy heart size may return to normal without extended bed rest. A compromise of a subdued life style is usually prescribed.

Acute alcohol intake alters myocardial mitochondrial and sarcoplasmic reticulum morphology and chronic alcohol abuse leads to perma-

nent destruction of myofibers with interstitial scarring. Thus the treatment of cardiomyopathic patients must include the avoidance of all alcohol. Discontinuation of alcohol after chronic abuse is associated with a gradual improvement of myocardial function over an eight week period. Before crediting any therapy with improvement of the status of patients with alcoholic cardiomyopathy one must be sure that no alcohol has been consumed for at least two months.

Vasodilator therapy for heart failure is presently enjoying popularity. Several investigators have recommended consideration of the physiol-

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The increased coronary blood flow may enable some borderline ischemic regions of the subendocardium to repair hypoxic damage. The salvage of such areas may improve ventricular performance. These possibilities are currently being investigated.

The weakness of our study is the absence of patient controls. Because of the heterogeneity of COCM, a controlled study would have to be very large to match etiologies, age, ventricular function and pressures. Nevertheless, a study should be performed in which patients would be randomized to control (digitalis and diuretics) would be used in all groups, vasodilator therapy, inotropic therapy, and combined vasodilators and inotropes. Such a study could recognize which patients benefit from each type of therapy in symptoms, function and longevity.

The therapy of congestive heart failure is expanding and dobutamine would appear to have a significant role. Whether the therapy should be a single three day infusion, intermittent or even continuous infusions is undecided. Finally, an oral inotrope with properties similar to dobutamine would be of great value in the drug regimen of COCM.

Summary

Dobutamine was given intravenously for three days to 38 patients with congestive cardiomyopathy. The patients were followed by serial determinations of functional class and by non-invasive measurements of left ventricular function, systolic time intervals (PEP/LVET) and echocardiogram (%ΔD). The average functional class (FC) of this group was 3.8 prior to dobutamine, but two days after completion the average FC was 2.7. By four weeks the average FC was 3.1 and by 10 weeks it was 3.4.

The average PEP/LVET declined significantly ($p < 0.001$) at three days, four and nine weeks and at 10 months after the discontinuation of dobutamine infusion. Also, 67% (20 of 30) of patients had improvement of the PEP/LVET by greater than -0.04 at seven days. Even two and six months after dobutamine, 58% (15 of 26) and 39% (seven of 18) were improved. Similarly, the %ΔD was improved by at least 2° in 60% (18 of 30) at seven days and 55% (16 of 29) at four weeks. At two and six months, 50% (14 of 28) and 42% (10 of 24) were improved. Those patients who did not improve their FC were more likely (five of nine) to

have left ventricular free wall thickness (by echocardiogram) less than 0.5 cm/M. Those who responded usually (22 of 29) had a ventricular wall thickness greater than 0.5 cm/M. Although the mechanism of the prolonged improvement after a three day infusion of dobutamine is not understood, this study suggests that dobutamine has a role in the therapy of chronic congestive heart failure.

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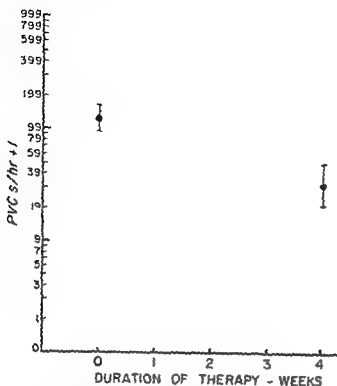


Fig 1 An illustration of the results of short term (4 weeks) acebutolol therapy on the incidence of PVCs. Standard error of the mean is used in all instances.

weeks of therapy all patients had a second chest x ray and repeat ophthalmological testing. All 20 patients had serum levels of acebutolol and its active acetyl metabolite measured approximately two to four hours after the last dose of the drug according to the method of Meffin and associates.⁴ The serum drug level estimations coincided with the day of the four week Holter recording.

At the time of entry into the study 14 of 20 patients had a prior history of myocardial infarction with stable angina pectoris. Two patients with a prior history of myocardial infarction had no post infarction angina. All patients with prior myocardial infarction were at least three months post myocardial infarction at the time of the study entry. Four patients with no history of prior myocardial infarction had stable angina. None of the patients had unstable angina at the time of study entry. Five patients had had saphenous vein bypass surgery performed at least one year prior to study entry for angina pectoris resistant to conservative medical management. All 20 patients were in New York Heart Association Functional Class I or II without clinical evidence of congestive heart failure. However, four of 20 patients had on baseline chest x ray a cardiothoracic ratio of greater than 50%. All 20

patients had normal renal and hepatic function. No patient had a positive ANA titer prior to study entry.

On baseline electrocardiogram remote transmural myocardial infarction was present in eight of the 20 patients. In the remaining 12 patients, the electrocardiogram was either normal or revealed only nonspecific ST-T changes. One patient had complete right bundle branch block. No A-V block or resting heart rates of less than 60 beats per minute were observed in any of the patients.

At the time of entry into the study, seven of 20 patients had no symptoms suggestive of cardiac arrhythmia and were selected for the study on the basis of frequent premature ventricular contractions noted on 12 lead electrocardiograms during routine clinic visits. One patient had a copal spells unrelated to postural change or a bolus abnormality or neurological disease. Twelve patients had unexplained diurnal spells with or without palpitations.

The 24 hour Holter tapes were analyzed on the Model 660 A Avionics electrocardiograph and the following features were quantitated: (1) the number of PVCs expressed as the number per hour; (2) the number of episodes of paired PVCs; and (3) the number of episodes of PVCs in runs of three or more. For the purposes of this study, three or more consecutive PVCs at a rate in excess of 120 beats per minute were considered to represent ventricular tachycardia. Similar runs at rates between 60 and 120 beats per minute were considered to represent accelerated idioventricular rhythm. The Model 660 A Avionics electrocardiograph allowed playback of the tapes at speeds of 1, 30, 60, and 120 times real time. To detect and quantitate ventricular arrhythmias, we used oscilloscopic display of one or two simultaneous channels of electrocardiographic leads, the R-R interval, and an R wave triggered scan system and the Avionics arrhythmia analyzer. The arrhythmia analyzer employed variable characteristics of prematurity, QRS width, and amplitude to detect and quantitate ventricular ectopy. The frequency of ventricular ectopy was expressed as the number per hour and displayed on the scanner and a trend printout record showed the hourly count of ventricular ectopic beats. In addition, all tapes were manually scanned and all areas of questionable accuracy were verified by direct writeout and hand recording with evaluation of these rhythm strips by

The long-term suppression of ventricular arrhythmia by oral acebutolol in patients with coronary artery disease*

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Beta blocking agents have enjoyed increasing popularity in managing post myocardial infarction patients since long term prophylactic administration of beta blocking agents to survivors of myocardial infarction has been shown to result in a decreased incidence of sudden death. Many beta blocking agents with claims for less effects than propranolol on noncardiac beta receptors are currently undergoing clinical evaluation. Acebutolol [(±) 1 (2 acetyl 4 butyramido phenoxyl) 3 isopropylamino propan 2 ol hydrochloride] a relatively cardioselective adrenergic receptor blocking drug with weak sympathomimetic activity is one such drug. Even though its efficacy when used both parenterally and orally in treating ventricular ectopy over a short period has been shown in several studies, the long term efficacy and safety of oral acebutolol has not been well documented.

Material and Methods

Patients for this study were selected on the basis of the presence of a minimum of 10 PVCs

per hour (mean) present on a single 24 hour Holter monitor performed after discontinuing digitalis and antiarrhythmic drugs for at least one week. During the entire study period patients continued to remain without concurrent therapy with digitalis preparation or other antiarrhythmic drugs. Only patients with documented coronary artery disease were eligible for selection for the study. Patients with congestive heart failure, symptomatic chronic obstructive lung disease, insulin dependent diabetes, and significant ophthalmological disease were also excluded. Due to untoward effects noted with other beta blocking agents on the eye,* all patients being considered for the study had detailed ophthalmological testing by an ophthalmologist and any patient with a significant ophthalmological problem was excluded.

After obtaining informed consent, 20 male patients with an average age of 57 years and a minimum of 10 PVCs per hour (mean) on baseline Holter monitoring had complete physical examination, chest x ray, 12 lead electrocardiogram, and laboratory tests including an antinuclear antibody (ANA) titer performed at baseline. Oral acebutolol was then commenced at a dose of 100 mg orally every eight hours and was continued for four weeks. During this period, weekly 24 hour Holter monitoring was performed using a two channel Avionics Model 445 electrocardiogram recorder. The daily dose and the frequency of acebutolol were adjusted depending on the effect of the drug on the PVC frequency noted during weekly Holter monitoring. At the end of four

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Table 1 Results of acebutolol therapy on PVC incidence

| Pt no | Short term trial | | | | | | | Dose | Side effects |
|-------|------------------|-----------|-----|---------|-----------|-----|-------|---------------------|--------------|
| | Control | | | 4 weeks | | | | | |
| | PVC/hr | PVC pairs | PVT | PVC/hr | PVC pairs | PVT | | | |
| 1 | 14 | ~ | ~ | 1 | ~ | ~ | 600 | ~ | |
| 2 | 996 | 42 | 2 | 162 | 14 | ~ | 1,200 | ~ | |
| 3 | 86 | 1 | ~ | 20 | ~ | ~ | 900 | GI intolerance | |
| 4 | 101 | ~ | ~ | 11 | ~ | ~ | 1,200 | ~ | |
| 5 | 50 | ~ | ~ | 7 | ~ | 1 | 900 | GI intolerance | |
| 6 | 57 | 2 | ~ | 15 | ~ | ~ | 900 | ~ | |
| 7 | 53 | ~ | ~ | 0 | ~ | ~ | 900 | ~ | |
| 8 | 1,797 | 86 | ~ | 275 | ~ | ~ | 1,200 | GI intolerance | |
| 9 | 118 | ~ | ~ | 1 | ~ | ~ | 1,200 | ~ | |
| 10 | 641 | 36 | ~ | 8 | ~ | ~ | 1,200 | ~ | |
| 11 | 108 | ~ | ~ | 1 | ~ | ~ | 1,200 | ~ | |
| 12 | 477 | 44 | 1 | 529 | 12 | ~ | 1,600 | GI intolerance | |
| 13 | 24 | ~ | ~ | 13 | ~ | ~ | 300 | ~ | |
| 14 | 179 | ~ | ~ | 369 | ~ | ~ | 1,200 | ~ | |
| 15 | 110 | 31 | ~ | 97 | 36 | 1 | 1,200 | Mild GI intolerance | |
| 16 | 167 | 1 | ~ | 190 | 2 | ~ | 1,200 | ~ | |
| 17 | 75 | ~ | ~ | 186 | ~ | ~ | 1,200 | ~ | |
| 18 | 100 | ~ | ~ | 67 | 1 | ~ | 1,200 | ~ | |
| 19 | 131 | 6 | ~ | 181 | 9 | ~ | 1,200 | ~ | |
| 20 | 65 | 6 | ~ | 163 | 23 | ~ | 900 | ~ | |

Abbreviations: CHF = congestive heart failure; GI intolerance = gastrointestinal intolerance; PVC = premature ventricular contractions; PVT = premature ventricular tachycardia.

therapy to a geometric mean number of 32 PVCs per hour ($P < 0.005$). However, when the responses of the individual patients were considered, PVC reduction from baseline values was greater than 90% in four patients and greater than 70% in 11 of 20 patients. In the remaining nine patients, PVC reduction from baseline values was less than 50%. In fact, in six of these nine poorly responding patients, there was no reduction in PVCs from baseline values (Table 1).

In six patients with paired PVCs at baseline, paired PVCs were noted after four weeks of acebutolol therapy in four patients (Table 1). Three of these four patients were nonresponders (patients showing less than 70% total PVC reduction). Even though the two patients with baseline PVT had no PVT following therapy, the other patients without PVT at baseline had one to three beat episode each of PVT after four weeks of acebutolol therapy. Again, one of these two latter patients was a nonresponder.

In all 20 patients, the mean serum level of acebutolol was 759 ± 351 (standard deviation) ng/ml. The corresponding serum level of its acetyl metabolite was $1,756 \pm 797$ (SD) ng/ml,

giving a metabolite to unchanged acebutolol of 2.3:1. The mean serum levels of acebutolol and its metabolite in the 11 patients responding greater than 70% PVC reduction were 723 ± 289 ng/ml and $1,807 \pm 783$ (SD) ng/ml, respectively. These levels were not significantly different from the nonresponders, 796 ± 411 (SD) ng/ml acebutolol and $1,707 \pm 811$ (SD) ng/ml acetyl metabolite.

No syncope or near syncope was noted during therapy in any patient. All 11 patients responding greater than 70% total PVC reduction remained free or became free of symptoms suggestive of cardiac arrhythmia after therapy. However, since only highly subjective symptoms, i.e., palpitations and dizzy spells, were noted in our patients, the effect of acebutolol therapy on symptoms suggestive of arrhythmia cannot be adequately evaluated from the present study.

The mean resting heart rate at baseline in patients was 77 beats per minute and after 4 weeks of therapy, 63 beats per minute ($P < 0.001$). The mean heart rate before and after acebutolol therapy in the 11 responders

cardiologist During analysis of the data the term complex PVCs was used to mean an arrhythmia with two or more of the following features during the 24 hour Holter monitoring greater than 10 PVCs per hour paired PVCs and paroxysmal ventricular tachycardia (PVT)

These data were analyzed by use of Student's *t* test In comparing means across time the paired *t* test was used In comparing groups of responders versus non responders the unpaired *t* test was applied For the PVC data a variance stabilizing transformation was applied to the data before analysis by the *t* test This transformation amounted to adding the number one to each PVC count and then taking the natural logarithm (essentially this amounts to testing for significant differences among geometric rather than arithmetic means)

During the four weeks of therapy acebutolol was administered on a thrice daily schedule in 12 of the 20 patients and on a four times daily schedule in the remaining eight patients The average daily dose of acebutolol used in the 20 patients during the four week trial was 1 100 mg (range 600 to 1 600 mg)

In order to determine the long term efficacy and safety of the drug nine of the 11 patients responding with greater than 70% PVC reduction from baseline values during the four weeks of acebutolol therapy who consented to join the long term evaluation were continued on acebutolol for 12 months The two patients who did show a satisfactory response at the conclusion of the short term study who were excluded from the long term study were one patient who left the state of Arkansas and was not available for long term participation and a second who decided not to participate in a long term study for personal reasons During the 12 months of therapy all patients returned for 12 lead electrocardiograms and physical examinations every four weeks At the 1 month 4 month 8 month and 12 month visits all patients in addition had 24 hour Holter monitoring chest x ray laboratory tests including an ANA titer and detailed ophthalmological testing During the long term evaluation the acebutolol dosage and frequency were adjusted depending on the clinical response and the frequency of ventricular ectopics as noted on the serial 24 hour Holter monitor recordings

The average daily dose of acebutolol used in the long term trial was 1 300 mg (range 600 to 1 600 mg per day) The acebutolol was administered on

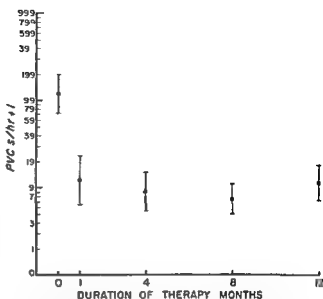


Fig 2 An illustration of the response of long term acebutolol therapy 0 = PVC incidence at baseline (pre drug) Standard error of the mean is used in all instances

a thrice daily basis in three of the nine patients and on a four times daily schedule in the remaining six patients The characteristics of the nine patients on the long term trial were as follows (1) average age 56 years (2) all had stable angina pectoris (3) six of nine patients had had prior myocardial infarction not less than three months prior to study entry and (4) four of nine patients had had prior saphenous vein bypass surgery at least one year prior to study entry

Of the nine long term subjects three were free of symptoms suggestive of cardiac arrhythmia at baseline Six patients has unexplained dizzy spells with or without palpitations prior to starting acebutolol therapy None of the long term study patients gave a prior history of syncope or cardiac arrest

The Holter recordings performed on the long term evaluation were analyzed in the same way that the short term Holter recordings were analyzed and the same arrhythmia characteristics were quantitated

Results

Short term trial (four weeks of therapy) The results of short term acebutolol administration in the 20 patients studied are shown in Fig 1 When the response to therapy of the whole study group was considered the geometric mean number of PVCs per hour in the 20 patients before therapy (125) was significantly lowered by acebutolol

Table II Complex PVCs during therapy in all nine patients

| | >10 PVCs/hr | Paired PVCs | PVT |
|------------------------------|-------------|-------------|--------|
| Baseline | 9 pts | 5 pts. | 1 pt |
| 12 month visit | 5 pts | 2 pts | 0 pts. |
| At least once during therapy | 8 pts | 4 pts. | 2 pts |

PVC = premature ventricular contraction PVT = number of episodes of paroxysmal ventricular tachycardia.

nificant fluctuations in PVC counts once therapy was commenced.

Prior to acebutolol therapy the geometric mean number of PVCs per hour in the nine study patients was 117 and at the 12 month visit the geometric mean number of PVCs per hour was 11 ($P < 0.001$). The geometric mean number of PVCs noted at the 1 month 4 month 8 month and 12 month Holter recordings was nine per hour and was not significantly different from the geometric mean number of PVCs at the 12 month visit (11 per hour).

After 12 months of acebutolol therapy the percentage reduction in PVCs noted at the 12 month visit was greater than 90% in four of nine patients greater than 80% in six patients and greater than 60% in seven patients. One patient had a 46% reduction in PVCs and one patient had no reduction in PVCs at the 12 month visit. This patient who did not respond to long term acebutolol therapy who also happened to have the smallest number of baseline PVCs (14 per hour) had excellent PVC control through eight months of therapy and showed a sudden unexplained increase in PVCs to 58 per hour at the 12 month visit (Table I).

Even though over all decrease in PVCs was impressive complex features of ventricular ectopy persisted despite acebutolol therapy in some patients. This is shown in Table II in which it can be seen that greater than 10 PVCs per hour and paired PVCs persisted during therapy in some patients. Paired PVCs present at baseline in five patients were abolished on the four Holter recordings during therapy in only two patients. PVT was abolished in the one patient having PVT at baseline. However in two other patients PVT was noted during therapy. Each of these two patients had one three beat episode of PVT each on a single Holter recording done during therapy. One of these patients also had one episode of accelerated idioventricular rhythm during therapy.

However all patients remained symptom free in spite of these observations.

As was observed during the short term intervals on the 12 lead ECGs were not significantly changed before and during long term acebutolol therapy. Significant beta blockade apparent even during long term therapy by fact that the mean resting heart rate fell from baseline mean value of 79 beats per minute in nine patients to 62 beats per minute after months of acebutolol therapy. No symptoms bradyarrhythmias were encountered during long term trial. During long term therapy no ocular or hematological side effects were observed.

Discussion

Previous studies using acebutolol both orally and parenterally have shown that acebutolol both safe and effective over a short period in patients with PVCs.² The present study shows that in the small number of patients studied, initial therapeutic response can be expected to be maintained over the long term in the majority of patients with safety. In nine of the 11 patients satisfactorily responding to the four week trial of acebutolol and who consented to participate in the long term acebutolol trial for 12 months greater than 80% PVC reduction was maintained through one year of therapy in two-thirds of the patients. Recent cardiovascular literature focused on the limitations of 24 hour electrocardiographic monitoring in evaluating the efficacy of antiarrhythmic agents mainly due to the day-to-day variability of PVC incidence in patients with cardiac arrhythmia.³ Using two 24-hour Holter recordings an approximately 80% reduction from baseline values is thought to be sufficient statistically for establishing therapeutic efficacy in antiarrhythmic drug evaluation. Thus using these stringent criteria it can be seen that in the majority of the patients in the present study long term acebutolol therapy did maintain a greater than 80% PVC reduction through the initial 12 months of therapy.

This study also shows that of the nine of patients who failed to respond to acebutolol therapy satisfactorily six patients had an increase in PVCs following acebutolol therapy. An excellent response or no response with respect to antiarrhythmic efficacy has been suggested previously with propranolol therapy. Our results

| <i>Long term trial</i> | | | | | | | | | | |
|------------------------|------------------|------------|----------------|------------------|------------|-----------------|------------------|------------|-------------|---------------------|
| <i>4 mo</i> | | | <i>8 month</i> | | | <i>12 month</i> | | | <i>Dose</i> | <i>Side effects</i> |
| <i>PVC/hr</i> | <i>PVC pairs</i> | <i>PVT</i> | <i>PVC/hr</i> | <i>PVC pairs</i> | <i>PVT</i> | <i>PVC/hr</i> | <i>PVC pairs</i> | <i>PVT</i> | | |
| 5 | — | — | 1 | — | — | 58 | — | — | 600 | — |
| 23 | — | — | 5 | — | — | 56 | 3 | — | 1,200 | — |
| 46 | — | — | 40 | — | — | 33 | — | — | 600 | — |
| 73 | — | — | 5 | — | — | 1 | 1 | — | 1,200 | — |
| 29 | — | — | 17 | — | — | 2 | — | — | 1,200 | Alopecia |
| 7 | — | — | 11 | 2 | — | 8 | 3 | — | 1,600 | Impotence |
| 1 | — | — | 1 | — | — | 1 | — | — | 900 | — |
| 1 | — | — | 1 | — | — | 1 | — | — | 1,600 | — |
| 0 | — | — | 34 | 4 | — | 1 | — | — | 1,600 | — |

tients showing greater than 70% PVC reduction) was 80 beats per minute and 63 beats per minute respectively ($P < 0.001$) and in the nine non responders it was 73 and 63 beats per minute respectively ($P < 0.001$). However the difference in the bradycardic response following acebutolol therapy between the 11 responders and the nine non responders was not statistically significant.

The mean systolic blood pressure before and after four weeks of acebutolol therapy was 131 and 126 mm Hg respectively (not significant). Similarly no significant differences were noted in the PR interval, the QRS and the corrected QT interval following short term acebutolol therapy. None of the patients had atrioventricular block during therapy. One patient developed a single episode of accelerated idioventricular rhythm during sleep. However a further increase in the dose of acebutolol in this patient subsequently did not result in a recurrence of this arrhythmia. No symptomatic bradyarrhythmias were noted in any of the patients.

Side effects during short term therapy (Table 1)—Four patients experienced evidence of tran-

sient mild gastrointestinal intolerance which did not need dosage adjustment of acebutolol. One patient developed a 1 cm increase in heart size on chest x ray with a decreased exercise tolerance after two weeks of acebutolol therapy. However the addition of a diuretic agent quickly reversed both the symptoms and the cardiomegaly. No hematological or ocular side effects were noted during short term therapy in any patient.

Effects of short term acebutolol therapy on angina—All 17 of 20 patients thought to have stable angina by history prior to entering the study had significant subjective decrease in angina following acebutolol therapy. However no objective measurements of angina relief by the drug in the form of exercise testing was carried out during the study.

Long term trial

The response to long term acebutolol therapy over 12 months in the nine patients is depicted in Fig 2. This figure shows a highly statistically significant and consistent decrease in PVCs from baseline values which was then maintained throughout the 12 month period with only insigni-

dose of propranolol.¹⁴ In the present study the concentration of the acetyl metabolite after oral administration of acebutolol was consistently higher than the plasma concentration of the parent compound. Similar results have been reported earlier by Winkle and colleagues.¹⁵

With potential benefits in the management of hypertension¹⁶ and angina,¹⁷ as well as cardiac arrhythmia,¹⁸ beta blocking agents such as acebutolol enjoy a unique role in treating patients with organic heart disease where the triad of angina, hypertension and cardiac arrhythmia often coexist even though the efficacy of acebutolol in each of these three conditions is yet to be well established. The results of the present study, along with the other studies on the short term use of acebutolol as an antiarrhythmic agent suggest that this drug may become a useful addition to the clinician's currently inadequate antiarrhythmic armamentarium.

Summary

The short term efficacy of oral acebutolol was evaluated in 20 patients with coronary artery disease and frequent premature ventricular contractions (PVCs) by serial 24 hour Holter monitoring before and while the patients were receiving an average daily dose of 100 mg of acebutolol for four weeks. Fifty five percent of the 20 patients showed a greater than 70% PVC reduction from baseline values. The only serious side effect during short term therapy was mild reversible cardiac decompensation in one patient. The long term safety and continued efficacy of acebutolol was then evaluated over the next 11 months in nine of the 11 patients showing greater than 70% PVC reduction at four weeks. Two thirds of these nine patients continued to show greater than 50% PVC reduction from baseline values at 12 months. One patient developed a pericarditis during long term therapy. The majority of patients not responding well to acebutolol at four weeks had an actual increase in PVCs on acebutolol therapy. We conclude that acebutolol produces long term effective reduction in PVCs without serious toxicity in the majority of patients with ventricular ectopy. However this drug appears to either produce an excellent response or no response with regard to PVC control in most instances.

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suggests a similar tendency with acebutolol since 5% of the 20 patients showed a greater than 70% VC reduction and 30% had no reduction in VCs from baseline values. However a larger patient population will have to be studied before definite conclusions can be drawn in this regard since beta blocking agents have been shown to be most beneficial in patients displaying evidence of increased activity of the autonomic nervous system with resting tachycardia.¹¹ It is possible that patients with ventricular ectopy and slower resting heart rates tend to have a less dramatic response to therapy with beta blocking agents with regard to antiarrhythmic efficacy. However in our group of 20 patients even though both of the 11 responders and the nine non responders did demonstrate a significant bradycardic response from baseline levels the difference in the decrease in heart rate between the two groups was not statistically significant. Thus an excessive bradycardic response or a lack of a bradycardic response cannot be said to explain why 55% of our 20 patients showed an excellent response and the remaining 45% showed a poor response or no response. Since the serum levels of the drug and its acetyl metabolite were not significantly different in these two groups of patients drug toxicity or inadequate blood levels cannot be said to be the cause of this excellent or poor response with no tendency to obtain intermediate results with acebutolol therapy.

Even though the total abolition of complex characteristics of ventricular ectopy such as pairing runs of PVC and greater than 10 PVCs per hour was not observed with acebutolol therapy in the long term trial it must be considered that the patients in the study population had only sporadic episodes of runs of PVCs both at baseline and during drug therapy and a separate study using patients with more serious and more frequent episodes of ventricular tachycardia will have to be studied before a judgment on the efficacy of acebutolol in suppressing complex ventricular arrhythmia can be reached. However the present study does suggest that in the small group of patients studied acebutolol is effective in significantly reducing the incidence of isolated PVCs in the majority of patients.

Before the safety of acebutolol with long term use can be fully evaluated a much longer experience using a much larger patient population than has been observed in the present study will have to be evaluated. However in the present study

the only patient who needed to have the drug discontinued due to side effects was the single patient who developed alopecia. Alopecia has also been noted rarely as a side effect of propranolol therapy. The remaining side effects noted were either transient or were reversed by simple counteractive measures without decreasing the acebutolol dosage or stopping the drug. Ocular side effects noted with practolol,³ another beta blocking agent were notably absent with acebutolol in spite of closely monitoring patients for such side effects. Likewise no hematological side effects were observed.

The present study was not designed to evaluate the relative cardioselectivity of acebutolol. Hence in our study the effects of the drug on pulmonary functions could not be commented on since pulmonary functions were not evaluated objectively with spirometry and blood gas determinations and none of the patients had symptomatic chronic obstructive pulmonary disease. However the absence of respiratory symptomatology in our 20 patients during acebutolol therapy is noteworthy. Decalmer and colleagues¹ have reported that most of the so called cardioselective beta blocking agents including acebutolol when given to patients with bronchial asthma do produce some impairment of ventilatory function. But their effects are less depressant in patients with bronchial asthma than the non cardioselective beta blocking agents such as propranolol.

Even though patients with prior or current cardiac decompensation were excluded from the present study one patient developed mild easily reversible symptoms suggestive of congestive heart failure during the four week trial of acebutolol. Thus as with other beta blocking agents patients with borderline states of cardiac compensation who require therapy with drugs such as acebutolol will have to be observed carefully for evidence of cardiac decompensation.

Measurement of serum levels of acebutolol the parent compound and its acetyl metabolite revealed no significant difference in the serum level of either agent between the patients responding adequately and the remaining non responders. Adequate therapeutic levels for antiarrhythmic efficacy of acebutolol have yet to be worked out fully. But the wide range of plasma levels of both agents measured regardless of the therapeutic response and dose is similar to the lack of correlation between plasma propranolol levels in different patients given the same oral

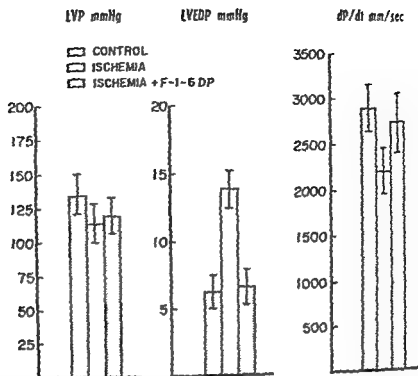


Fig 1 The effect of fructose-1,6-diphosphate (FDP) on left ventricular pressure (LVP), left ventricular end-diastolic pressure (LVEDP) and the rate of ventricular pressure rise (dp/dt) when administered intravenously at 45 minutes after onset of acute myocardial ischemia in 10 dogs. The administration of FDP continued as a constant infusion at the rate of 1.25 mg/kg/minute until the termination of the experiment (see text). The standard errors of the mean are indicated.

the femoral vein was used for administration of FDP and other drugs and fluids. Prior to induction of ischemia, arterial pO_2 , pCO_2 , pH and CO_2 combining power were verified as to whether they were in physiologic range and if not appropriate adjustments of respiratory volumes and rates were made.

Acute myocardial ischemia was induced by either ligating or obstructing a major branch of the left coronary artery with a balloon catheter.

Open chest. In 10 dogs the heart was suspended in the pericardial sac after thoracotomy and the left anterior descending artery (LAD) was dissected free. A control period of 1 hour was allowed prior to ligation of the LAD. During this period ventricular and aortic pressures, cardiac output measurements and epicardial ECG tracings were recorded. The epicardial ECG recordings were unsatisfactory (even though we used cotton wick electrodes suspended on a spring) because artifacts due to motion caused by the respirator made them unreliable. Therefore after the ligation of the LAD the chest was closed and precordial ECG was monitored throughout the experiment. In this group five animals received

FDP and five controls received equimolar dextrose intravenously.

Closed chest. In 10 closed chest dogs myocardial ischemia was induced by inflating a balloon of a Swan Ganz catheter placed under fluoroscopic guidance either in the LAD or in the circumflex artery. Such an arrangement permits constant monitoring of the coronary perfusion pressure during the occlusion and assessment of the reperfusion in the ischemic muscle segment by pre- and post-occlusion monitoring of the ^{86}Kr clearance. The volume of the ^{86}Kr solution was 0.5 ml and the injectate of 0.9% NaCl solution was 2 to 2.5 cc. These solutions do not have a significant effect on the heart rate given by themselves over periods of 10 seconds during occlusion. In this paired series for the open chest preparations five animals received FDP and the others received equimolar dextrose at the same infusion rate via the femoral vein.

Ischemic period (45 minutes). Once the chest had been induced, arterial blood samples were taken for gas and pH determinations at 15, 30, and 45 minutes. In some animals arrhythmias were treated with an intra-

Experimental and laboratory reports

Hemodynamic, electrocardiographic, and metabolic effects of fructose diphosphate on acute myocardial ischemia

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The myocardial district distal to an arterial obstruction rapidly becomes ischemic and only a limited period of time is available to restore sufficient energy production before the damage becomes irreversible. It has long been hoped to fill such a void in anaerobic energy production in the ischemic myocardium by stimulation and acceleration of the Embden Meyerhof pathway. This has been done experimentally and clinically administering quantities of glucose, insulin and potassium. Since Sodi Polares and associates first reported success with such therapy for acute myocardial infarction many clinical and experimental contradictions have arisen and both the results and the hypotheses used to support early and present claims have in one way or another been challenged.¹⁻⁴ The most important criterion raised and experimentally documented is that the Embden Meyerhof pathway catabolic activity is not increased but rather impaired by the progressive inactivation of several enzymes in the course of acute myocardial ischemia.⁵⁻⁷ A critical step in ischemic inhibition of glycolysis appears to be inactivation of phosphofructokinase induced by progressively increasing intracellular acidosis,⁸⁻¹⁰ thus depriving the pathway of fructose 1,6-diphosphate (FDP). One approach to relieve this would be to provide FDP exogenously. Such

an increase in the cytoplasmic concentration of FDP should stimulate glycolysis by intervening as a metabolic regulator and substrate to permit function at higher rates. This study was designed to determine experimentally whether such biochemical intervention offers real advantages in protection of acutely ischemic myocardium. Two major questions are addressed: (1) does intravenous administration of FDP stimulate glycolysis and improve energy production and mechanical function of ischemic myocardium and (2) will this metabolic intervention result in practical benefit and have eventual application in modifying the extent of the ischemic injury in the heart muscle?

Methods

Twenty five mongrel dogs* were used in this study. After sedation with morphine sulfate 15 mg (subcutaneous) general anesthesia was induced with pentobarbital 30 mg/kg given intravenously. The animals were secured in the left lateral decubitus position intubated and ventilated with a respiratory pump with the use of ambient air. Both carotid and jugular veins were dissected free and were used to place catheters under fluoroscopic guidance into the left ventricle, pulmonary artery, left anterior descending (LAD) or circumflex (CFX) artery and right atrium. Another catheter was advanced through a femoral artery to the aortic root while

The animals used in this study were maintained and used in accordance with the Animal Welfare Act of 1970 and the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Sciences National Research Council.

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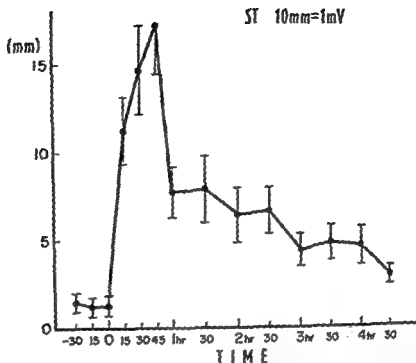


Fig 3 Precordial ST-segment elevation after coronary occlusion and the effect of FDP intravenous administration which began at 45 minutes after the onset of ischemia. Values shown are means \pm SE (10 dogs).

myocardium were also analyzed for cytochrome oxidase (cyt a_1)¹⁰ and lactate dehydrogenase activity.¹⁰

In five normal anesthetized animals FDP was given intravenously in doses ranging from 100 mg to 2 gm./kg. (from 20% stock solution) in order to verify whether this compound has any hemodynamic effects. In two animals we studied the ATP and CP in the heart and other organs while in the remainder we studied not only hemodynamic parameters but the plasma half life of FDP and blood lactic acid concentration as well. Also the effect of FDP on the dog erythrocyte metabolism both *in vivo* and *in vitro* was assessed. This consisted of measuring the ATP and 2,3 DPG content of the erythrocytes and comparing the contents to those that were incubated with glucose.

Results

Hemodynamics. Occlusion of one of the major branches of the left coronary artery resulted in a drop in mean arterial pressure and left ventricle systolic pressure while the left ventricular end diastolic pressure (LV EDP) began to rise progressively (Figs 1 and 2). The cardiac output also decreased significantly from 4.86 ± 0.56 L./minute to 2.77 ± 0.21 L./minute during the ischemic period. Within 7 to 11 minutes after the intrave-

nous administration of FDP the LV EDP began to decline from 13.82 ± 3.3 mm Hg and stabilized at 6.8 ± 2.0 mm Hg until the termination of the experiment (Fig 2). The FDP administration caused the left ventricular and aortic pressure to rise but they never reached control level (Fig 2). The same trend was exhibited by the dp/dt (Fig 1). The negative dp/dt reflected the relaxation phase which also improved after the FDP administration. The cardiac output after the FDP administration began to increase progressively and in about 15 to 20 minutes after the administration of FDP it attained a value of 4.4 ± 1.1 L./minute and remained there until the termination of the experiment. The ^{86}Kr clearance of the ischemic region in the closed-chest animals was 11.82 ± 1.6 ml./min./100 gm., while the control flows were in the range of 1.4 ± 0.4 ml./min./100 gm. By the end of the fourth hour ^{86}Kr clearance increased to 19.36 ± 2.1 ml./min./100 gm. Of the 10 control animals, three died and two had no significant hemodynamic or ECG changes. In the rest the mechanical function of the heart deteriorated progressively.

Effect of FDP on ECG. In some of the untreated and treated closed-chest animals there was a marked elevation of the ST segment prior to occlusion. We attributed this ST segment elevation to

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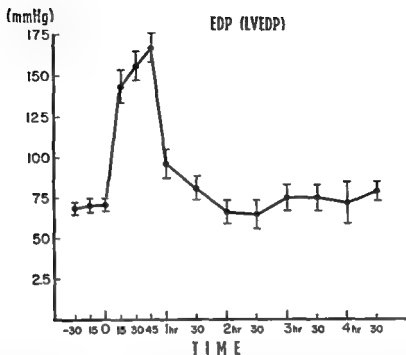


Fig 2 The time response of left ventricular end diastolic pressure (LVEDP) to intravenous administration of FDP in 10 dogs with acute myocardial ischemia. The FDP administration began at 45 minutes after the onset of ischemia. The most pronounced decline of LVEDP was observed during the first 15 minutes after the FDP was given.

olus of lidocaine only during the 45 minute period. After FDP or glucose administration had been started (i.e. at 45 minutes) no drugs were given except for a maintenance dose of anesthetic. During this period cardiac output measurements using the thermodilution technique were made at 15 minutes, 20 minutes, 30 minutes and at 45 minutes and concurrently the other hemodynamic and electrophysiological data were recorded. In the closed chest group the coronary blood flow measurements were made 1 minute prior to occlusion and at 30 minutes of ischemia.

Ischemia + FDP intervention. At 45 minutes of ischemia administration of FDP was started via the femoral vein using a Harvard infusion pump at the rate of 1.25 mg/min/kg. A stock solution of 5% FDP prepared 30 minutes prior to administration from fructose 1,6 diphosphate sodium salt (Sigma Chemical Co., chemical grade 1:1) was stored in a refrigerator. The control animals (10) received 5% dextrose in water at the same rate. For the next 4 hours (i.e. 4 hr and 45 minutes after onset of ischemia) both the treated and control animals received only FDP and glucose at precisely specified concentrations and

rates. During this period ^{86}Kr clearance determinations from the ischemic region were made every 30 minutes while hemodynamic and electrophysiological parameters were monitored constantly on a DR Electronics for Medicine recorder. Recordings of these data were made every 15 minutes; cardiac output determinations were made every 30 minutes. At the conclusion of each study (4 hr and 45 minutes) or following ventricular fibrillation the chest was opened and transmural sections from the ischemic and normally perfused myocardium were taken with a specially designed cutting tool that had been cooled in liquid nitrogen. These myocardial tissue samples were used for ATP, CP, lactate and histochemical studies.

The frozen transmural sections of both normal and ischemic myocardium were homogenized in 6% perchloric acid and the supernatant was used to determine ATP, CP and lactate tissue content. The ATP and CP were assayed with the method described by Lamprecht and co-workers^{16, 17} and the tissue lactate was assayed by the method of Marbach and Weil.¹⁸ Sections from ischemic and normally perfused

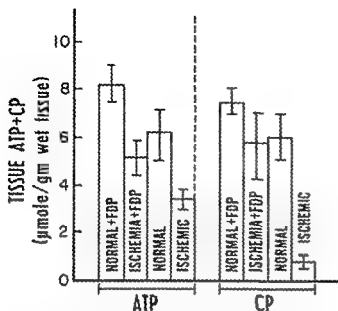


Fig 5 Effects of fructose 1,6 diphosphate (FDP) on high energy phosphates in the normally perfused and ischemic myocardium (10 dogs). The effects of FDP on myocardial tissue content of adenosine triphosphate (ATP) and creatine phosphate (CP) are compared to the control group that received equimolar dextrose (labelled normal and ischemic). Each column represents the mean \pm SD.

normal and ischemic myocardium (before cytotoxicity occurs) (2) as a means of indirectly monitoring the oxygen deficit in the ischemic myocardium demonstrated by the low activity of the reduced form of cytochrome a_3 . Histochemically, the activity of cytochrome a_3 in ischemic tissue was very diminished in both treated and untreated animals (except for the two control dogs that had no hemodynamic nor ECG changes) while LDH activity appeared the same for both groups.

The effect of FDP in normal animals. In five normal anesthetized dogs the plasma half life was found to be 18.53 ± 1.62 minutes. The disappearance rate of FDP when added to dog blood at 37°C was 76% less than when FDP was administered intravenously. This indicates that approximately 24% is taken up by the erythrocytes and hydrolyzed prior to being taken up by the different tissues. The ATP content of the erythrocytes in the blood incubated for 30 minutes at 37°C was two times higher compared to those that were incubated with equimolar glucose. The 2,3-DPG concentration in erythrocytes *in vivo* and *in vitro* studies was elevated to the same degree as observed for the A11. Intravenous administration of a total of 500 mg/kg over 10 minutes in three anesthetized dogs caused the plasma lactic

acid to double within one hour (from 6.21 ± 1.4 mg% to 12.8 ± 1.98 mg%) while in most tissues including the heart the ATP and CP contents were elevated.

Discussion

The glycolytic flux in acute myocardial ischemia in the dog is increased ten to fifteenfold during the transition from aerobic to anaerobic energy production.¹¹⁻¹³ This can supply up to 60% of the energy needs of the ischemic myocardium. Phosphofructokinase activity appears to be a limiting factor for glycolysis as shown by the accumulation of glucose 6 phosphate and fructose 1,6 phosphate.¹⁴⁻¹⁶ Fructose 1,6 diphosphate (FDP) is an intermediate substrate in glycolysis. Its depletion in the course of acute ischemia is due to the inactivation of the highly pH sensitive enzyme phosphofructokinase (PFK) which many investigators^{14-16, 17} have attributed to failure of glycolysis to proceed in such conditions. The low activity of PFK can be best explained by its properties. Kubler and Speckermann¹⁸ have shown that the activity of PFK is less resistant in experiments with cardioplegia and anoxic perfusion than in ischemic cardiac arrest where lactate production is very slow. This implies that PFK is a highly pH dependent enzyme (cofactor similar to that of Mansour¹⁹). The metabolic acidosis that has taken place inhibits the PFK; however when the lactic acid has been washed out from the myocardium and acidosis is corrected Kubler and Speckermann¹⁸ have observed reactivation of PFK. The studies of Mansour¹⁹ in heart phosphofructokinase also confirm that PFK is highly sensitive to acid pH. At the very late stage of ischemia glycolysis is again a function of PFK activity simply because there is not enough ATP for phosphorylation of fructose 1,6 diphosphate although there is increased concentration of glucose 6 phosphate and fructose 6 phosphate.

As PFK appears to be the limiting step in anaerobic glycolysis the hexokinase and the phosphorylase are of no interest if FDP is the initial step but phosphoglycerate dehydrogenase needs a constant supply of NAD to function. In ischemic conditions when glucose is the substrate there is no accumulation of NADH due to the decreased activity of PFK rather than of pyruvate kinase (PK). It is very important to note that pyruvate

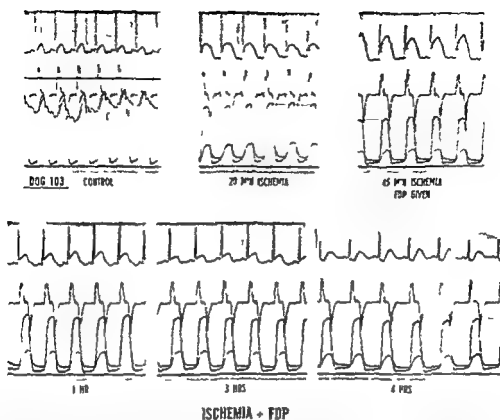


Fig 4 Representative tracing of the electrocardiographic hemodynamic changes in the closed-chest induced acute myocardial ischemia. On the tracing are recorded the precordial ECG, left ventricular pressure, dp/dt , and peripheral coronary pressure. Note the regression of ST segments after the FDP intervention (pressure calibration is 1 mm. = 1 mm. Hg)

he control period to partial coronary artery obstruction by the Swan Ganz catheter (Fig 3). Once the balloon was inflated or the LAD ligated the ST segment began to rise until FDP was given. Within 5 to 7 minutes after the administration of the FDP the ST segment began to decline initially very rapidly for about 20 minutes but later it was less pronounced (Figs 3 and 4). Three of the dogs of the control group (10) that received 5% dextrose in water fibrillated (at 1 hr and 14 minutes, 1 hr and 32 minutes and at 2 hr and 46 minutes). In five of these animals the precordial ECG demonstrated progressively increasing myocardial injury while in two dogs of the same group only depression of the ST segment was noted after ligation of the LAD. After FDP administration began no arrhythmias were observed in any of the treated animals.

Effect of FDP on ATP, CP and lactate in ischemic and normally perfused myocardium. The ATP content in the ischemic muscle segment of the non treated animals showed about 50 to

60% deficit while creatine phosphate (CP) was very low. The absolute values of myocardial tissue content of ATP, CP and lactate are given in Fig 5. One may notice that in normally perfused myocardium in dogs treated with FDP there was also a noticeable increase in ATP and CP (Fig 5). The tissue lactic acid in the group that received FDP was higher in the normally perfused myocardium than that found in the group that received 5% dextrose in water (Fig 6).

This difference in tissue lactic acid content found in the ischemic muscle in the treated animals was double that found in the ischemic muscle segment of the controls (Fig 6).

Histochemical results. Although these results are not quantitative and do not influence to a great extent the conclusion of this study, they were used for the following reasons. (1) In ischemic myocardium the cytochrome c (cyt c) activity is very low while dehydrogenase (LDH) levels are t

dium These results indicate that FDP intervenes in the Embden Meyerhof pathway not only as a high energy substrate but also as a metabolic regulator influencing the activity of phosphofructokinase and that of pyruvate kinase FDP also stimulates glycolysis in dog erythrocytes and increases their ATP and 2,3 DPG content by a factor of 2

The most significant finding in these studies is that this biochemical intervention appears to restore the depressed activity of glycolysis in ischemic myocardium

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kinase needs FDP as an allosteric cofactor which directly stimulates its activity. This influence of FDP on pyruvate kinase activity has been observed in the liver²² developing embryo²³ and in yeast.^{27, 28} When PFK is activated there is no available FDP which is needed for the PK to operate at optimal reaction velocity for the production of pyruvate hence no substrate for lactate dehydrogenase to generate NAD. Therefore it appears that the presence of FDP is necessary not only as a substrate but as a metabolic regulator in order for the glycolysis to function at the level of the trioses.

Another important catalytic activity of FDP is its direct feedback action on phosphofructokinase (PFK). The activity of PFK is stimulated by ADP, AMP and inhibited by ATP, citrate¹ and acidosis. FDP in high concentration removes this inhibition of ATP, citrate¹ and acidosis. This has been shown in this study and indirectly supported by the fact that the FDP administration in man induces lactic acid increase and increased glucose utilization.^{31, 32} Theoretically such an increase in ATP/ADP ratio induced by the FDP disinhibition of PFK could be maintained as long as an excess of FDP exists in cytosol in both normally perfused or ischemic tissue (provided that there is still some residual flow). The other advantage of using FDP as a substrate in acute ischemia and any energy deficient states is obvious: the rate limiting enzymes above PFK are eliminated and those below are no longer inhibited. From an energetic point of view the advantage of using FDP as the initial substrate for glycolysis is that the net yield of the anaerobic metabolism of one mole of glucose is 2 ATP while if one mole of FDP is metabolized in the same conditions it will produce 4 ATP because there is no phosphorylation of glucose and fructose 6 phosphate reactions which require utilization of ATP. On the other hand while doubling the quantity of ATP produced lactate production remains the same as though one mole of glucose had been metabolized. It is obvious that in order to obtain the same results in the direction of making usable energy available from FDP it is necessary to administer it in large quantities (on the order of several grams). (The LD₅₀ of FDP when administered at the rate of 500 mg/minute in dogs is approximately 5.8 to 6 gm/kg.)

Another important finding in this study is that

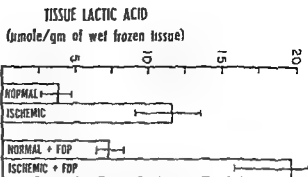


Fig. 6 The mean myocardial tissue lactate content in the normally perfused ischemic myocardium for the group that received 5% dextrose in water (the two columns on the left) and the group that was treated with fructose 1,6-diphosphate (FDP) on the right. Note that the value for ischemic myocardium from the dogs that received FDP is almost double that found in the controls.

FDP causes a substantial increase of 2.3 DPG in the erythrocytes. This increase of 2.3 DPG is of importance for the oxygen exchange between hemoglobin and tissue. It also contributes, perhaps in a lesser manner, by increasing the oxygen available to the marginal heart muscle surrounding the ischemic tissue.

The results of this study demonstrate that FDP when given to dogs with experimentally induced acute regional myocardial ischemia improves the mechanical function of the heart, causes regression of electrocardiographic ischemic changes and increases significantly the ATP and creatine phosphate in both ischemic and normally perfused myocardium. Extrapolating from these results it appears that FDP can indeed restore the depressed activity of the Embden Meyerhof pathway in ischemic myocardium.

These conclusions suggest a rational basis for employing FDP in clinical situations as an agent to limit or decrease infarct size in acute myocardial infarction.

Summary

The hemodynamic, electrocardiographic and metabolic responses of dogs with acute myocardial ischemia to intravenous administration of fructose 1,6-diphosphate (FDP) were assessed.

Analysis of the results (compared to dextrose control) revealed evidence of major improvement of LVEDP and cardiac output, significant decrease of the ST segment and large increases of ATP and CP in the ischemic district and to a lesser degree in the normally perfused myocardium.

Table I Study groups with myocardial ischemia

| | Non treated control | Aspirin treated | Indomethacin treated |
|----------------------------|---------------------|-----------------|----------------------|
| Number of animals | 36 | 20 | 20 |
| Hemodynamics | 8 | 10 | 9 |
| ECG mapping | 18 | 10 | 9 |
| Platelet Cr and In studies | 11 | 4 | — |
| Tissue electrolytes | 9 | 8 | 9 |
| Plasma FFA | 8 | 7 | 9 |

before the induction of ischemia the balloon was inflated with 1 ml of air and peripheral coronary pressure was monitored using a Statham strain gauge. Complete coronary occlusion was evidenced by a reduction of mean peripheral coronary pressure to approximately 30 mm Hg and by the appearance of an injury potential on standard Lead I. No antiarrhythmic drugs were used and animals that fibrillated within the initial 15 minute high risk period were excluded from the study. Thus four animals of the non treated group, three of the indomethacin treated group and one of the aspirin treated group were excluded from the study. These eight animals were not included in the group of 76 animals shown in Table I. The experiment was designed for a four hour ischemic period during which hemodynamic parameters and electrocardiograms were continuously monitored and were intermittently recorded along with cardiac output. Estimated size of the ischemic area was made during the four hour period from 20 precordial ECG leads determining the number with ST elevation (NST) and the sum of the ST elevation (EST) using an electrical calibration of 0.1 mV. Serial arterial blood samples were taken from both groups for the plasma free fatty acid determination method. As described before,¹¹ microcirculatory thrombosis was determined at the end of the four hour balloon occlusion by taking multiple myocardial tissue samples from the region of the obstructed coronary artery and the contralateral non ischemic area from animals preinfused with ⁵¹Cr or ¹¹¹In. Microcirculatory thrombosis was expressed as the radioactivity ratio of the multiple tissue samples taken from the ischemic and non ischemic areas.

At the conclusion of the studies the thorax was incised and the heart was rapidly arrested with iced Ringer's solution. The ischemic area of the

left ventricle was excised parallel to a diagonal branch 1 cm below the obstruction site down to the apex and then perpendicular to the anterior descending artery across to the termination of the most inferior diagonal branch or an unobstructed extension when this branch terminates short of the apical level. The outer margin was formed by the termination of the main epicardial segment and the other diagonal branches. This formed an approximately triangular shaped sample with the base at the cardiac apex and the peak 1 cm below the obstruction site. In previous studies we have observed that injection of Evans Blue distal to the obstruction site at diastolic pressure levels stains this area except where there is aberrant vessel distribution.¹² Such animals were excluded from this study. A similar size segment approximating 12 g was taken from the non ischemic posterior wall. In view of the potential heterogeneity of the myocardial metabolic response the ventricle was divided into inner and outer layers: the tip of the papillary muscle was excluded and the epicardial adipose tissue was removed. To analyze for sodium and potassium concentrations samples were homogenized and extracted for 48 to 72 hours in distilled water sufficient time for complete extraction. Potassium and sodium were determined in duplicate on an Auto Analyzer system with flame attachment. Water content was determined by drying samples in an oven at 100 °C to constant weight.

In evaluation of the results the study was divided with regard to precordial ECG mapping, tissue analysis for electrolytes and water and plasma free fatty acid levels. For statistical analysis Student's *t* test for paired and non paired observations was used when appropriate. Mortality rates were assessed by the χ^2 formula.

Results

Table I summarizes the groups studied as well as the number of animals and the procedures used to assess the effects of aspirin and indomethacin in the animals subjected to a four hour thrombotic coronary occlusion. For the presentation of results the number of animals used from each group was felt to be adequate for providing statistically analyzable information with comparable numbers of animals among the groups and for each category of parameters. Compensatory hemodynamic changes during the four hour

Chronic use of aspirin versus indomethacin during non-thrombotic myocardial ischemia effects on survival

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Our previous studies on the effects of chronic treatment of aspirin (ASA) upon acute non thrombotic coronary occlusion in dogs showed that this analgesic was effective in significantly decreasing the incidence of ventricular fibrillation associated with a reduction of sodium and water accumulation and potassium loss in ischemic tissue. On the other hand recent reports on indomethacin an analgesic with action upon platelet function and prostaglandin metabolism described as similar to that of ASA^{2,3} showed that when given acutely ischemia induced by coronary ligation was enhanced.³ In view of this disparity as well as other differences related to the regulation of myocardial blood flow⁴ we have utilized a closed chest canine model to study the effects of chronic treatment with indomethacin upon arrhythmias during non thrombotic coronary occlusion and compare its effectiveness with that of ASA.

Methods

A total of 76 apparently healthy male mongrel dogs weighing 20 to 26 kilograms were used and were divided into two groups. Group A (N = 20) treated with aspirin 600 mg daily and Group B

(N = 20) treated with indomethacin 25 mg /day. The doses of the two drugs are moderate therapeutic schedules calculated on the basis of body weight. Both groups were treated for seven consecutive days prior to the day of the experiments. A group of 36 dogs served as non treated controls. After an 18 hour fast all animals on the day of the experiment were anesthetized with morphine sulfate (3 mg/kg intramuscularly) and sodium pentobarbital (20 mg/kg intravenously) and were subsequently placed on a respiratory pump to maintain adequate ventilation. Frequent pH determinations were performed to confirm maintenance within the physiologic range. The left jugular vein and left and right carotid arteries were exposed through small skin incisions. Number 8F catheters were passed into the left ventricle via the right carotid artery and the root of the aorta via the femoral artery. Left ventricular and aortic pressures were recorded by means of Statham strain gauge transducers using an Electronics for Medicine DR 8 amplifier recorder. Cardiac output was determined by the thermodilution technique with the thermodilution catheter placed in the main pulmonary artery via the jugular vein.⁵ All animals were under continuous electrocardiographic monitoring.

Myocardial ischemia was induced by means of a double lumen balloon tipped catheter inserted through the left carotid artery and positioned under fluoroscopic control in the left anterior descending coronary artery approximately 2.5 cm from its origin as described before.¹ After determining control hemodynamic parameters

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Table IV Left ventricular electrolytes after four hours of ischemia

| | $H_2O\%$ | | | | | | Na ($\mu\text{Eq/g}$) | | | | | | K ($\mu\text{Eq/g}$) | | | | | |
|-------------|---------------|-----------|-----------|-----------|-----------|-----------|-------------------------|-----------|-----------|-----------|-----------|-----------|------------------------|-----------|-----------|-----------|-----------|-----------|
| | Untreated (9) | | ASA (8) | | Indo (8) | | Untreated (9) | | ASA (8) | | Indo (9) | | Untreated (8) | | ASA (9) | | Indo (8) | |
| | N | I | N | I | N | I | N | I | N | I | N | I | N | I | N | I | N | I |
| | | | | | | | | | | | | | | | | | | |
| Inner layer | 80.6 | 84.4 | 77.3 | 80.4 | 79.4 | 82.2 | 36.7 | 64.0 | 38.0 | 57.0 | 45.7 | 67.4 | 71.9 | 33.0 | 61.0 | 48.0 | 73.3 | 33.3 |
| | ± 0.5 | ± 0.6 | ± 0.9 | ± 1.0 | ± 0.4 | ± 0.5 | ± 1.2 | ± 8.7 | ± 2.0 | ± 4.1 | ± 2.1 | ± 4.3 | ± 2.0 | ± 2.5 | ± 2.2 | ± 3.7 | ± 3.3 | ± 3.3 |
| Mid layer | 81.0 | 83.5 | 78.1 | 79.7 | 79.4 | 82.3 | 36.3 | 67.0 | 36.0 | 52.0 | 42.1 | 60.7 | 69.6 | 38.0 | 69.6 | 54.0 | 71.1 | 33.3 |
| | ± 0.5 | ± 0.4 | ± 0.6 | ± 1.0 | ± 0.5 | ± 0.9 | ± 1.0 | ± 7.4 | ± 1.6 | ± 3.2 | ± 2.6 | ± 3.6 | ± 0.9 | ± 3.9 | ± 0.6 | ± 3.3 | ± 3.3 | ± 3.3 |
| Outer layer | 80.4 | 83.7 | 77.7 | 79.1 | 78.3 | 79.8 | 37.2 | 72.0 | 37.0 | 50.0† | 44.2 | 54.4 | 72.7 | 46.0 | 78.0 | 56.0 | 70.4 | 33.3 |
| | ± 0.5 | ± 0.8 | ± 0.8 | ± 0.9 | ± 0.4 | ± 1.1 | ± 1.0 | ± 7.8 | ± 2.0 | ± 4.6 | ± 1.9 | ± 3.2 | ± 1.6 | ± 6.3 | ± 5.6 | ± 3.4 | ± 3.3 | ± 3.3 |

P = 0.01

†P = 0.05

when compared to both the non treated group and the indomethacin treated group ($P < 0.02$). Table VII shows radioactivity from labelled platelets in tissue samples from the ischemic and non ischemic areas indicating that only when thrombus was obstructing the left anterior descending coronary artery was there significant accumulation of platelets in the microcirculation, suggested by the significant ratio of ischemic to non ischemic tissue. With balloon obstruction there were no differences when compared to non treated or to aspirin treated animals.

Discussion

The results of the study suggest that in the absence of a thrombotic process in the coronary arteries aspirin pretreatment appears to be capable of modifying survival associated with balloon obstruction of the coronary artery. In contrast, pretreatment with indomethacin failed to reduce mortality rate which was the same as the one observed in the non treated animals. Analysis of the data obtained in the study indicates that whereas the hemodynamic changes were not consistent among the three groups myocardial injury following balloon occlusion appeared to be of lower magnitude in the aspirin group at the end of the four hour period when compared to its own control. Since water and cation changes after four hours of ischemia were less extensive in the aspirin group one could postulate on the contribution of more extensive tissue swelling in the non treated as well as in the indomethacin treated group contributing to local changes generating more intensive ischemia and higher incidence of fatal arrhythmias.

It should be noted that loss of potassium in the indomethacin group was the smallest among the three groups. Since in studies by others it has been shown that in the animals receiving indomethacin regional and collateral blood flow was decreased the observed decrease in potassium loss in the indomethacin group could be a related phenomenon. A lower perfusion could result in a greater accumulation of potassium leaked from the cardiac cell in the interstitium.

This study raises the question regarding the mode of action of the antiplatelet agents, at the cyclo oxygenase level, namely whether the action is indeed non selective affecting indiscriminately the enzyme responsible for the generation of the opposing prostaglandins stored in platelets and the vascular endothelium. Recent studies suggest that aspirin in small amounts blocks preferentially platelet cyclo oxygenase and therefore the generation of thromboxane-A₂ allowing its counterpart prostacyclin stored in the vascular endothelium to exert its vasodilating and platelet antiaggregating effect. This action was also implied by the studies of Caplan and colleagues who found that aspirin pretreatment increased collateral flow after coronary occlusion in dogs. In the studies of Korb and Moncada it was found that aspirin in doses of 150 mg/kg blocked both platelet and endothelial prostaglandin. However using 10 mg/kg these investigators described a net effect in favor of prostacyclin. The results obtained in our study could be relevant to the observation made by Korb and Moncada with their lower aspirin dose since the dose of 30 mg/kg, although lower than 10 mg/kg is still within the usual clinical

Table II Hemodynamic parameters

| | Control | | | 60 minutes | | | 4 hours | | |
|----------------------------|------------------|-------------|-------------|------------|---------|---------|-----------|----------|----------|
| | Untreated (8) | ASA (10) | Indo (9) | Untreated | ASA | Indo | Untreated | ASA | Indo |
| Heart rate (beats/min) | 147±9.0 | 131±7.9 | 155±17.9 | 147±8.1 | 176±6.7 | 149±6.1 | 130±9.3 | 120±8.6 | 147±6.8 |
| Aortic pressure (mm Hg) | 139±8.2 | 119±7.2 | 159±2.4 | 177±10.1 | 170±8.4 | 148±2.4 | 133±3.6 | 117±10.3 | 147±2.9† |
| LVEDP pressure (mm Hg) | 12±2.0 | 10±1.2 | 13±0.9 | 12±1.2 | 11±1.2 | 16±1.3† | 16±3.1 | 14±1.3† | 70±2.2 |
| SV (mL) | 271±5 | 178±2.5 | 245±2.2 | 244±1.2 | 162±1.4 | 251±3.0 | 160±1.9 | 148±1.6 | 200±1.8 |

P = 0.01

†P = 0.05

Table III Electrocardiographic mapping

| Time post-occlusion | 10 min | 1 hour | 4 hours |
|----------------------|--------------|--------------|--------------|
| NST | | | |
| Non treated | 14.00 ± 1.11 | 12.77 ± 1.23 | 13.53 ± 1.25 |
| Aspirin treated | 17.40 ± 1.52 | 11.7 ± 1.06 | 9.38 ± 1.34 |
| Indomethacin treated | 9.0 ± 0.53 | 8.0 ± 1.67 | 9.0 ± 1.09 |
| EST (mV) | | | |
| Non treated | 4.41 ± 0.4 | 4.21 ± 0.52 | 4.53 ± 0.73 |
| Aspirin treated | 6.25 ± 1.60 | 6.09 ± 1.33 | 4.23 ± 0.89 |
| Indomethacin treated | 3.56 ± 0.13 | 3.41 ± 1.09 | 3.69 ± 1.02 |

nary occlusion in the treated and non treated animals (Table II) aortic pressure in the indomethacin treated group appears to be at levels suggestive of hypertension as described side effect of indomethacin. Subsequently over the four hour period systemic pressure fell with a concomitant rise in the left ventricular end diastolic pressure to levels that were significant when compared to control. In contrast pressure changes in the non treated and aspirin treated groups were less consistent showing a significant end diastolic pressure rise in the aspirin group and a significant decrease in stroke volume in the non treated group. There were no significant changes in heart rate among treated and non treated groups. Precordial ECG mapping (Table III) showed that the degree of ischemia over the four hour period of observation remained practically unchanged from the non treated and the indomethacin treated animals whereas in the aspirin group there was a gradual decrease in the extent of ischemia although the observed differences were not statistically significant. Table IV shows changes in water content and

electrolyte concentrations in the ischemic cardiac tissue. In the aspirin treated group water accumulation was significantly less in all layers when compared to the non treated group. In the indomethacin group the increased tissue water was somewhat less than in the non treated group but more than in the aspirin treated group in the inner and middle layers. Sodium increments were of smaller magnitude in the aspirin treated group statistically significantly different from the non treated animals in the outer and mid layers. In the indomethacin group the gain of sodium was consistently more in all three layers. However while potassium loss from ischemic tissue was reduced in the aspirin group particularly in the endocardial layers it was even more so in the indomethacin group when compared to the non treated group. Free fatty acid determination in all groups showed that the expected rise in FFA in ischemia was aborted in the aspirin as well as the indomethacin treated animals (Table V).

Comparing mortality rates in the three groups (Table VI) it was found that in the aspirin treated group mortality rate was significantly less

sodium and water abnormalities of the ischemic tissue. These changes were not related to consistent abnormalities in hemodynamic parameters or evidence of microcirculatory thrombosis.

Summary

In view of the reported disparity of the effects upon ischemic myocardium of aspirin and indomethacin both affecting platelet function and prostaglandin metabolism we utilized a closed chest canine model to study the effects of chronic treatment with these agents upon arrhythmias during non thrombotic coronary occlusion. Group A (N = 20) and Group B (N = 20) were pretreated for seven consecutive days with aspirin 600 mg/day and with indomethacin 25 mg/day respectively. A group of 36 non treated animals served as controls. Determination of hemodynamics revealed no significant differences in left ventricular function among the various groups although blood pressure levels were consistently higher in Group B. Precordial ECG mapping showed lower magnitude of myocardial ischemia in the aspirin group. Changes in water and cation composition of the ischemic tissue after four hours of coronary occlusion were also significantly lower in the aspirin group suggesting that more extensive tissue swelling in the indomethacin group might have contributed by means of more intensive ischemia to a higher incidence of ventricular fibrillation. Consistently higher blood pressure levels requiring increased mechanical demands on the myocardium would enhance the negative results observed in the indomethacin group. Mortality rate was 5% for the aspirin group versus 40% and 39% for the indomethacin and the non treated groups respectively ($P < 0.015$). The failure to observe significant platelet accumulation by radioactivity counts in either treated or non treated animals using ^{51}Cr and ^{111}In labelled platelet indicated that microcirculatory thrombosis was not a feature in this model. It is not clear to what extent the reported diverse mostly inhibitory effects upon the various enzyme systems and lysosomal membrane ascribed to anti-inflammatory agents are applicable more for indomethacin per se or for the therapeutic schedule used in this study in order to explain its different effect upon ischemic myocardium.

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Table V Free fatty acid in treated and untreated groups ($\mu\text{Eq/L}$)

| | No | Before myocardial ischemia | After 4 hours coronary occlusion | P |
|--------------|----|----------------------------|----------------------------------|-------|
| Non treated | 8 | 210 \pm 38 | 696 \pm 246 | <0.05 |
| Aspirin | 7 | 232 \pm 46 | 287 \pm 42 | NS |
| Indomethacin | 9 | 437 \pm 60 | 519 \pm 80 | NS |

NS = not significant

peutic levels and much closer to them than the dose of 150 mg/kg. These observations are consistent with previous studies describing differences in the effect of aspirin and indomethacin upon platelet prostaglandin synthetase. It was found that aspirin induced a long lasting or irreversible inhibition of platelet prostaglandin synthetase whereas indomethacin inhibited the enzyme for only a short period of time which might have expectedly cancelled a favorable effect of a non-antagonized endothelial prostacyclin such as described for aspirin.^{13,14} These findings then could explain at least in part the beneficial effect observed in the aspirin treated group and the negative results observed in our indomethacin treated animals which were consistent with observations indicating the adverse effect of this prostaglandin inhibitor upon ischemic myocardium.⁸ Since the absolute level of blood pressure in the indomethacin treated animals was higher than that of the other groups the adverse effect of this parameter requiring increased mechanical demands on the myocardium will have to be also considered in explaining the negative results observed in the indomethacin group. Moreover it has been pointed out that prostaglandin inhibitors exert with plasma levels achieved with therapeutic doses such as used in our study, inhibitory effect upon a variety of other enzymes and cellular systems. Among anti-inflammatory agents indomethacin used as a reference compound was documented as affecting a host of enzymes¹⁵ and in addition to inhibiting prostaglandin synthetase was also described as blocking membrane transport of prostaglandins and therefore access to their environment and interference with protection of ischemic myocardium. Whether such inhibitory activity is more consistent among the other inhibitors for indomethacin per se at the doses given in our studies is not clear. However

Table VI Mortality in treated and untreated groups

| | N | Mortality | P |
|--------------|----|-----------|-------|
| Non treated | 36 | 14 (39%) | |
| INDO-treated | 20 | 8 (40%) | NS |
| ASA treated | 20 | 1 (5%) | 0.015 |

INDO vs ASA = 0.02.

Table VII Radioactive platelet distribution after four hour coronary occlusion

| | N | Radioisotope | Mode Of occlusion | LAD/C ratio |
|--------------------------|---|--------------|-------------------|-------------|
| Control | 4 | Cr | None | 1.0 |
| | 8 | In | None | 1.0 |
| Ischemic | 8 | Cr | Thrombus | 3.30 |
| untreated | 7 | Cr | Balloon | 1.30† |
| | 4 | In | Balloon | 0.93† |
| Ischemic aspirin treated | 4 | Cr | Balloon | 1.44† |

P < 0.01

†P = NS.

its reported diverse effects upon the various enzyme systems and lysosomal membrane could render the observed unfavorable effects of indomethacin upon ischemic myocardium plausible. It is worth noting that in most of the experimental studies with indomethacin the compound was administered to open chested or preinstrumented animals and the doses used were far in excess of suggested therapeutic levels per weight unit. In contrast the results in our studies were obtained by long term daily administration of indomethacin at conventional therapeutic doses in animals that remained intact throughout the treatment and experimental period.

The failure to observe significant platelet accumulation by radioactivity counts in either treated or non treated animals using ⁵¹Cr or ¹¹¹In indicated that microcirculatory thrombosis is not the issue in this model.

The aborted free fatty acid rise in both treated groups might also be discounted in explaining mortality rate differences among the treated groups. Presently the exact mode of action of the anti-inflammatory agents in this model and this species eludes a clear understanding. It appears then that pretreatment with relatively low dose of aspirin was accompanied by lower incidence of ventricular fibrillation and by lower degree of

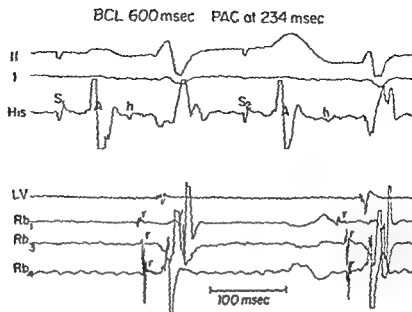


Fig 1 This figure shows the last of nine depolarizations that resulted from right atrial drive at 600 msec basic cycle length and also the depolarization produced by premature right atrial drive at 234 msec. Electrograms (from top to bottom) II and I represent electrocardiograms from ECG Leads II and I. His represents the recording from a His bundle catheter inserted into the aortic root. Deflection S_1 is the stimulus artifact. A is the atrial depolarization. h is the His bundle activation which is followed in turn by the activation of the high septal myocardium. and S_2 is the second and premature stimulus artifact. LV electrogram is recorded from bipolar electrodes in the left ventricular apex and shows some Purkinje activation and activation time of the left ventricle. Rb_1 electrogram shows the activation of the proximal right bundle (r) followed by activation of the underlying right ventricular septum. Rb_3 represents an electrogram 6 mm more distal on the right bundle showing right bundle activation (r) and mid right septal activation. Rb_4 represents the right bundle activation 9 mm more distal from the Rb_1 electrode. The second complex is premature and shows conduction delay above the His bundle (increased A-H interval) and conduction delay in the proximal right bundle branch of 15 msec.

the proximal right bundle as it emerged onto the surface of the right ventricular septum. A typical example of the activation sequence of a normal and premature beat is shown in Fig 1. The first complex shown represents the response to the last of nine regular stimuli given at 600 msec cycle lengths. Note that the His bundle activation is quickly followed by activation of the proximal right bundle branch (electrode Rb_1) and then at electrodes 6 and 9 mm more distal (Rb_3 and Rb_4). The muscle activation can be seen to occur earliest in the more distal right bundle electrodes and later near the proximal right bundle electrodes located in the upper right ventricular septum. The time of activation of both the right and left ventricular endocardium is nearly simultaneous. The second complex of Fig 1 is the least premature impulse that would not produce FRBBB. Note the similar activation of the second complex sequence to the first complex and compare the delay of conduction that occurs in

the proximal right bundle branch between electrodes Rb_1 and Rb_3 . The degree of conduction delay shown here is the maximum attained in nine experiments before blockage of conduction would occur.

Fig 2 shows the effect of making the premature stimuli more premature by only 4 msec in the same animal. The activation sequence is quite different in the second complex showing the FRBBB. There is no apparent activation of the right bundle distal to the most proximal electrode. The activation of the right ventricular myocardium now lags behind that of the right ventricle consistent with the delay of activation of the right ventricle. In these experiments, however, visualization of the activation front as recorded by the electrodes was never noted without seeing delay in activation of the right ventricular myocardium. In every instance of FRBBB produced in each of the nine experiments, the loss of recording of right bundle activation

Site of functional right bundle branch block

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There has been considerable speculation as to the site and mechanism of functional right bundle branch block (FRBBB). Certain investigators believe that the site of conduction block is at the distal end of the right bundle¹⁻³ while other workers favor a more proximal site.⁴⁻⁷ The present work was undertaken to document the site of functional right bundle branch by placing a 36-electrode plaque directly over the right bundle branch in an in vivo canine heart preparation and then recording the activation potentials both during normal conduction and during FRBBB.

Methods

Acute experiments were performed in nine mongrel dogs weighing 15 to 30 kilograms anesthetized with 30 mg/kg of phenobarbital. Artificial ventilation was maintained according to the 'Glenman and Radford nomogram'⁸ with a Harvard ventilator. A thermal blanket was used to maintain body temperature. Arterial and venous pressures were monitored throughout the experiment and volume replacement was given to maintain physiologic blood pressures. The heart was exposed by a midline sternal incision and the animal was anticoagulated with 10 000 units of heparin. The right heart was bypassed by collecting superior and inferior vena caval blood flow

into a cardiotomy reservoir and pumping this blood with a roller pump through a blood filter and then into the pulmonary artery. A more detailed description of this preparation is described elsewhere.⁹ With the heart empty of blood a 2 to 3 cm incision was made into the anterior right ventricular wall to expose the septum and the right bundle branch. A 10 by 15 mm plaque with 36 stainless steel flush electrodes was then sutured over the right bundle. The poles of the electrodes were separated by 15 mm across and 3 mm vertically. The plaque was positioned just lateral and inferior to the papillary muscle that inserts into the pulmonary conus and was superior and medial to the anterior papillary muscle. Up to six simultaneous bipolar electrograms could be monitored down the length of the right bundle at 3 mm intervals. After electrode placement the incision in the right ventricular wall was closed and the right heart bypass system was discontinued. Right bundle and His electrograms were recorded with a frequency response of 50 to 2 000 Hz. ECG leads were recorded at 0.2 to 2 000 Hz. Recordings were made on a light beam oscillograph at paper speeds of 25 to 200 cm/sec. The sinus node was crushed to allow for slower spontaneous heart rates. Driving and premature stimuli were of 2 msec duration and 15 times threshold in intensity to the right atrium via bipolar hook electrodes. At the termination of each experiment the location of the electrodes were confirmed by staining of the specialized conduction system with iodine solution.

Results

FRBBB was produced in nine dogs with high quality recordings from the right bundle branch by the 36-electrode plaque. In every case of FRBBB produced the conduction block was found to be located within the first 5 to 6 mm of

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hypoxic may play a role. The change in right bundle size as compared to the left bundle may result in loss of summation effects on conduction.

Summary

An in vivo canine heart was prepared by utilizing a temporary right heart bypass system to place close bipolar electrodes along the course of the right bundle branch. Activation within the right bundle could be recorded in up to six locations along the right bundle with premature supraventricular stimulation that caused functional right bundle branch block. The loss of activation recordings was found to occur in the proximal 0 to 6 mm of the right bundle branch in every instance and in nine different preparations.

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BCL 600msec PAC at 230msec



Fig 2 Electrograms are labeled similar to those in Fig 1 from the same experiment only 1 or 2 minutes later. The premature stimulus artifact is now 4 msec more premature. There is now functional right bundle branch block with block of activation beyond the most proximal right bundle branch electrode. There is delay of activation of the right muscle (compare activation time of right and left ventricular myocardium).

occurred in the proximal portion of the right bundle branch as it emerges onto the surface of the right ventricular septum.

Discussion

The occurrence of FRBBB on clinical tracings has generated considerable interest as to the site and mechanism of the conduction block. A search for the site of FRBBB has been recently stimulated by the reports of Myerburg and associates^{2,4} which utilized an *in vitro* canine myocardium and showed that the area of the specialized conduction system with the greatest refractoriness was 2 to 3 mm proximal to the Purkinje muscle junction. The physiologic role of prolonged refractoriness at the distal specialized conduction system could be consistent with a peripheral conduction block concept. Moe and co-workers³ however have provided indirect evidence suggesting that the site of FRBBB is more proximal. Elizari and colleagues were able to show a marked increase in action potential duration in the area of the proximal bundle branches and show slowing of conduction of premature impulses in this area. In *in vivo* canine heart preparations Zipes and associates have shown that the site of block is proximal to the false

tendon portion of the right bundle branch. Catheter recordings in man⁵ and dogs¹⁰ also support a proximal site of FRBBB. Our work more precisely documents the site of conduction block to be in the first few mm of the right bundle as it emerges into the right ventricular surface of the septum. In none of our experiments was the site of FRBBB located in the middle or distal portions of the right bundle branch. Our results also do not lend support to the concept of incomplete right bundle branch block at least in the healthy right bundle with premature stimulation methods. The maximum conduction delay prior to complete blockage of conduction was up to 15 msec duration in these studies. This is in contrast to the study by Elizari and co-workers who noted conduction delays of considerable magnitude using an *in vitro* preparation. The difference in our results may be due to the lack of normal perfusion in their experiments.

Our results confirm that the site of FRBBB is in the proximal right bundle branch. The possible causes of the conduction block in the proximal right bundle during FRBBB are unknown. Several possible mechanisms may be active. The change of perfusion from arterial blood to right ventricular cavity blood which is relatively

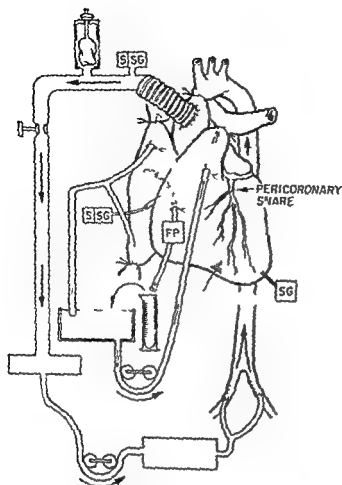


Fig 1 Diagram of the preparation. S = sampling site. SG = strain gage pressure transducer. FP = electromagnetic flow probe.

and connected to a Statham P23Db pressure transducer. The heart was exposed via a midline sternotomy. The internal mammary vessels were ligated bilaterally and the azygous vein, the pulmonary artery and the venae cavae were prepared for right ventricular bypass with umbilical tapes placed around each vessel. Two Teflon coated stainless steel wire pacing electrodes were introduced about 1 cm apart into the apex of the left ventricle (LV) and were then hooked against the endocardium. The electrodes were connected to a battery powered stimulator (Medtronic Inc. Model 5807). Complete atrioventricular block was induced by injection of 0.5 to 1 ml of 40% formaldehyde into the region of the AV node. The ventricular pacing rate was then set at 120/min.

A Satinsky arterial clamp was placed longitudinally on the anterior wall of the ascending aorta proximal to the origin of the brachiocephalic branch. A 1.5 cm longitudinal incision was made

in the anterior aortic wall, and a 16 mm woven Dacron graft was sutured along the incision using two 5-0 Prolene sutures.

A segment of the anterior interventricular (descending) branch of the left artery immediately distal to the origin diagonal branch was isolated and a tape snare was placed around it.

For right heart bypass as previously described¹¹ the pulmonary artery was cannulated using a No. 28F Foley catheter introduced into the vessel via a stab wound. The superior vena cava was cannulated the stump of the azygous vein with a Bardic cannula and the inferior vena cannulated via the right atrial appendage with a No. 32F Bardic cannula. The caval venous blood was drained by gravity into a plastic reservoir. The tip of another No. 32F catheter was placed in the inflow to the right ventricle. For completion of the pulmonary artery was ligated over the catheter (Fig. 1).

During right heart bypass drainage bypassed right heart chambers represent primary venous effluent minus LV. The venous effluent was diverted through an electromagnetic probe (Micron Instruments, Los Angeles) for continuous recording of coronary blood flow.

The pressure at the aortic root was monitored by ligating the ascending aorta between the Dacron graft and the origin of the brachiocephalic artery and diverting the entire LV (minus coronary blood flow) through the an extracorporeal circuit with a resistance (screw clamp) and capacitance (with equal parts of blood and NaCl 0.9%) blood was warmed in a heat exchanger and returned to the animal via cannulas in the femoral arteries using a second occlusion pump (Cardiovascular Instruments, W. Mass.). Using this technique the mean arterial pressure (MAP) was set at 70 mmHg during the remainder of the preparation.

The aortic root pressure was monitored side tube of the systemic circuit using a pressure transducer. LV pressure and its derivative (LV dP/dt) were measured with a catheter tip pressure transducer (Millar, Houston, Texas) introduced into the LV.

Effect of arterial pressure on left ventricular O₂ consumption, coronary blood flow and reserve capacity following coronary occlusion

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There has been considerable interest recently concerning the effects of changes in ventricular afterload on the extent of myocardial injury following coronary artery occlusion. Experimental studies suggest that a reduction in ventricular afterload by decreasing coronary perfusion pressure increases ischemic damage following coronary artery occlusion. However, clinical studies report a decrease in the predicted infarct size if in the course of acute myocardial infarction ventricular afterload is reduced. Also studies dealing with the effects of combination therapy with nitroglycerin and phenylephrine on the extent of ischemic injury during acute myocardial infarction have been contradictory. Thus there appears to be uncertainty regarding the effects of ventricular afterload changes on the extent of myocardial damage following coronary artery occlusion.

The methods commonly employed to assess the extent of myocardial injury involve ST segment mapping and serial analysis of serum CPK changes.¹ However recent studies suggest that ST segment changes following coronary artery occlusion may not accurately reflect the magni-

tude of myocardial ischemic damage.² Also controversy has arisen concerning the reliability of assessing infarct size from serum CPK changes alone.³ Furthermore these methods assess neither left ventricular functional impairment nor functional capacity of the remaining functional myocardium.

The present study was undertaken to evaluate the effect of different mean systemic arterial pressure levels on the reduction of left ventricular functional reserve capacity following the insult of coronary artery occlusion. Left ventricular functional reserve capacity was assessed by determining the tolerance of the left ventricle to increasing heart rate and to increasing resistance to ventricular ejection. Thus the heart rate and the systemic arterial pressure at which mean atrial pressure attained 12 mm Hg was used arbitrarily to define the limits of left ventricular functional reserve capacity.

Materials and methods

Mongrel dogs weighing 18 to 38 kilograms were anesthetized with intravenous sodium pentobarbital (30 mg/kg.) Following intubation with a cuffed endotracheal tube the animals were ventilated using a volume respirator (Harvard Apparatus Co. Dover Mass.) with 97% O₂ and 3% CO₂ and constant minute ventilation throughout each experiment. All animals received a continuous intravenous infusion of sodium bicarbonate 0.05 mM min⁻¹ kg⁻¹ of body weight for prevention of metabolic acidosis. Arterial pressure was monitored from the beginning of the study via a No. 8 catheter introduced into the left femoral artery.

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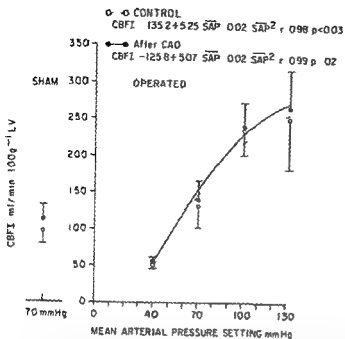


Fig 3 Coronary blood flow index (CBFI) changes in response to mean systemic arterial pressure setting before (control) and after coronary artery occlusion (CAO). Mean values \pm SE for each group of animals ($n = 5$). Curvilinear relationship of mean values was similar for both conditions.

define the lower limits of LVFRC by decreasing \overline{SAP} and HR. However when \overline{SAP} was steadily decreased the LAP usually decreased in similar fashion. Also at slower HR escape ventricular rhythms often intervened preventing substantial decreases in HR. Thus data describing the limits of LVFRC for lower \overline{SAP} and HR were not sufficient for statistical analysis.

In 25 animals prepared as described control data including assessments of LV functional reserve capacity were obtained. Each dog was then randomly assigned to one of five equal groups. One group in which \overline{SAP} was maintained at 70 mm Hg served as sham and the coronary artery although similarly prepared was not ligated. In the remaining four groups the \overline{SAP} was set at a new level of 40, 70, 100 or 130 mm Hg. After measurement of CBF and MVO_2 at the new pressure setting the previously isolated anterior descending coronary artery was occluded. Following coronary occlusion CBF and MVO_2 were determined at 5 minutes, 15 minutes and 30 minutes. These data were averaged for subsequent statistical evaluation since they did not vary significantly over time. After 30 minutes and while the coronary occlusion was maintained the \overline{SAP} was returned to its original control level

of 70 mm Hg. At this level CBF and MVO_2 again determined and LV functional reserve capacity was redetermined by the two techniques as described.

At the end of the experiment the heart excised and Evans blue dye was injected at low pressure into the coronary artery distal to the ligature. Immediately after injection the whole LV myocardium was excised and weighed for gross estimation of the non perfused LV myocardial segment. Subsequently the total LV weight was determined and was used for indexing the of the non perfused segment the CBF and MVO_2 , thus data obtained both before and after CAO were indexed to 100 g of total wet myocardium.

Statistical analysis was performed using analysis of variance for the five groups of data. The *t* test for paired observations for comparison data obtained in each animal before and after coronary occlusion and linear or polynomial regression analysis for estimating regression mean data values.

Results

There was no significant difference by analysis of variance in the indexed weight of stained myocardium following actual or sham coronary ligation (Table I). The mean percent for all dogs was 27.6 ± 1.0 of total LV myocardium.

Myocardial oxygen consumption and (MVO_2) values before and after coronary occlusion for the four groups in which the left anterior interventricular coronary artery was ligated, did not differ significantly by the *t* test for paired observations (Table II). In the sham operation group this MVO_2 difference was significant. MVO_2 mean values bear a linear relationship, the \overline{SAP} setting both before and after coronary occlusion (Fig 2). Since neither regression slope nor *y* intercepts differed significantly, the common predictive equation derived is:

$$MVO_2 \text{ ml } O_2/\text{min } 100 \text{ g }^{-1} \text{ LV} = 2.71 + 0.103 \overline{SAP} \text{ mm Hg } r = 0.99 \text{ } p < 0.001$$

Coronary blood flow index (CBFI) values before and after coronary occlusion did not differ significantly in any of the experimental groups (Table II). CBFI mean values bear a curvilinear parabolic relationship to the \overline{SAP} both before and after coronary occlusion (Fig 3). The predictive quadratic equation derived for values is:

apex. The pressure signal of the catheter tip transducer was matched with the pressure signal obtained via the lumen using a conventional P23Db pressure transducer. A No. 11 catheter was placed in the left atrium (LA) via the LA appendage and pressure was monitored using a P23Db transducer. Zero pressure reference was set at the mid right atrial level for all transducers.

A fiberoptic catheter was placed in the proximal coronary sinus via the right atrial appendage and was connected to an In Vivo oximeter (Phy-Med Control Seattle Wash.) for continuous monitoring of oxyhemoglobin saturation of coronary sinus blood and for periodic blood sampling.

The mean (SAP) and phasic aortic pressure, the left ventricular pressure (LVP), the coronary blood flow (CBF) signal, the coronary sinus oxygen saturation (ScsO₂) signal, a vertical body surface ECG lead and the LV dp/dt were recorded using an oscillographic recorder (Honeywell 1612 Denver Colo.). The temperature of the animals as measured directly from the posterior surface of the heart was maintained at 36.8 ± 0.2 °C through adjustment of warm water flow through the heat exchanger.

The flowmeter signal of coronary blood flow (CBF) was calibrated before each determination by repetitive (five to eight) timed collections (30 seconds) of the continuous siphon drainage of the right ventricle.

Blood samples were obtained from the arterial circuit and from the coronary venous drain and were iced immediately for determination of O₂ content by the Van Slyke method.¹¹ The pH, pO₂ and pCO₂ of blood samples were determined using the Astrup apparatus. The hemoglobin concentration of the samples was also determined. Myocardial oxygen consumption (MVO₂) was derived as the product of the CBF and the corresponding arteriovenous oxygen difference and was then indexed to 100 g of total LV myocardium (MVO₂I). Wet LV weight was determined at the conclusion of the experiment after excision of the atria along the atrioventricular groove and the right ventricle along its attachment to the interventricular septum.

Experimental protocol. Left ventricular functional reserve capacity (LVFRC) testing was conducted as follows:

1. With the HR set at 120 min⁻¹, the resistance of the arterial extracorporeal circuit was gradually increased at a constant rate by tightening the

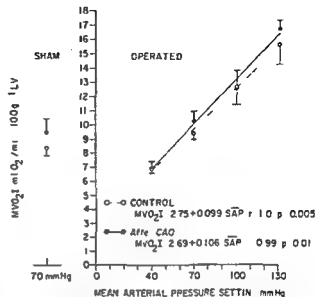


Fig. 2 Myocardial O₂ consumption index (MVO₂I) changes in response to mean systemic arterial pressure setting before (control) and after coronary artery occlusion (CAO). Mean values ± SE for each group of animals (n = 5). Linear relationship of mean values was similar for both conditions.

Table 1 Estimated percent of non perfused LV myocardium following coronary artery occlusion in each five animal group

| Mean systemic arterial pressure setting during coronary artery occlusion (mm Hg) | | | | | |
|--|------------|------------|------------|------------|----|
| 40 | 70 | 100 | 130 | 70 (Sham) | p |
| 96.6 ± 1.7 | 30.8 ± 1.9 | 24.2 ± 1.4 | 25.6 ± 2.7 | 30.7 ± 2.2 | NS |

p = Derived by analysis of variance

screw clamp thereby increasing the SAP until the mean LA pressure (LAP) rose to at least 14 mm Hg but not more than 16 mm Hg. The slope of SAP versus LAP was then derived by linear regression analysis of corresponding data points and the SAP at which the LAP attained 12 mm Hg was designated as the pressure limit of the LVFRC.

2. With the SAP set and maintained at 70 mm Hg, the ventricular pacing rate was steadily increased until the LAP rose to the above values. The slope of the HR versus LAP was similarly derived and the HR at which the LAP attained 12 mm Hg was designated as the HR limit of the LVFRC.

In each experiment attempts were made to

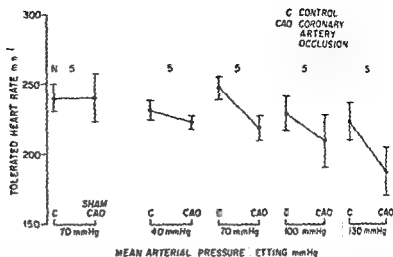


Fig 5 Tolerated heart rate resulting in mean left atrial pressure of 12 mm Hg before (control) and after minutes of coronary artery occlusion (CAO) at the indicated mean systemic arterial pressure setting. Tolerated heart rate range after CAO is not significantly affected by the level of pressure setting. However the mean values of tolerated heart rate bear a negative relationship ($r = 0.95$) to the pressure setting

Before coronary occlusion the results of the control assessment of LV functional reserve capacity as tested by increasing HR, did not differ among the five groups (Fig 5). For all 25 dogs the mean HR at which the LAP attained 12 mm Hg was 234.5 ± 4.6 min.

Following 30 minutes of coronary occlusion in the four groups with coronary ligation LAP of 12 mm Hg was attained during LV functional reserve capacity testing at a HR which was lower than control by an average of 23.1 ± 4.7 min ($p < 0.001$) (Fig 5). Although the magnitude of this reduction was not significantly different among the four groups by analysis of variance there was a slight trend (0.4 min⁻¹ per mm Hg) for the mean group values of these post occlusion estimates to correlate negatively with the SAP setting of the group. In the sham group the results of the control and post sham occlusion evaluations of LV functional reserve capacity by HR did not differ.

Discussion

Critique of method The criterion of 12 mm Hg of left atrial pressure for defining the limits of LV functional reserve capacity was set arbitrarily; however Braunwald and colleagues¹ reported this to be the upper limit of normal for resting humans. Furthermore in these and in similar previous experiments we observed that when LAP reaches this level as a result of rapid heart rate systemic arterial pressure increase or coro-

nary artery ligation its rate of rise is abrupt leading to rapid deterioration in LV function.

We utilized changes in heart rate and arterial pressure to test LV functional reserve capacity because such changes can be independently assessed. A similar approach was used in HR and afterload was used previously by several investigators in both the clinical and experimental setting.¹⁶⁻¹⁸ Quinones et al¹⁶ employed changes in preload and afterload to changes in HR and afterload to achieve the same goal.

Although it has been adequately demonstrated that after deprivation of blood supply myocardial contractile function occurs within seconds¹⁹⁻²⁰ the time for retesting LV functional reserve capacity following coronary artery occlusion was set at 30 minutes. We elected coronary ligation instead of the coronary artery occlusion model because the latter although more sensitive in depicting effects of hypoxia involves only transient hypoxia, not sufficient to the purposes of this study. We felt that 30 minutes represented sufficient time for the ischemic tissue and vasculature to be exposed to the systemic arterial pressure setting opposite effects on O₂ supply and demand afforded by the systemic arterial pressure point either in the direction of preservation of function although not necessarily of long term tissue viability.

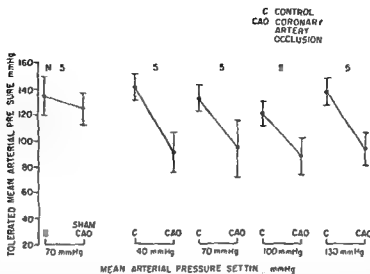


Fig 4 Tolerated mean systemic arterial pressure in mm Hg resulting in mean left atrial pressure of 12 mm Hg before (control) and after 30 minutes of coronary artery occlusion (CAO) at the indicated mean systemic arterial pressure setting. Tolerated pressure after CAO is not affected by the level of pressure setting

Table II Myocardial oxygen consumption and coronary blood flow indices before and after coronary artery occlusion

| | Mean systemic arterial pressure setting during coronary artery occlusion (mm Hg) | | | | |
|-----------------------------------|--|--------------|--------------|--------------|--------------|
| | 40 | 70 | 100 | 130 | 70 (Sham) |
| MVOI | | | | | |
| (ml O ₂ /min 100 g LV) | | | | | |
| Control | 6.90 ± 0.26 | 9.48 ± 0.53 | 12.64 ± 1.17 | 15.79 ± 1.44 | 8.30 ± 0.60 |
| Post coronary artery occlusion | 6.99 ± 0.39 | 10.30 ± 0.65 | 12.66 ± 1.20 | 16.82 ± 0.60 | 9.49 ± 0.91 |
| Mean difference | 0.10 ± 0.34 | 0.80 ± 0.11 | 0.02 ± 0.47 | 1.03 ± 0.98 | 1.14 ± 0.37 |
| | NS | NS | NS | NS | < 0.05 |
| CBFI | | | | | |
| (ml/min 100 g LV) | | | | | |
| Control | 52.8 ± 5.57 | 131.7 ± 30.0 | 234.9 ± 33.6 | 253.2 ± 68.0 | 97.3 ± 16.6 |
| Post coronary artery occlusion | 54.5 ± 4.6 | 140.2 ± 26 | 238.8 ± 34.3 | 266.8 ± 51.6 | 113.4 ± 18.7 |
| Mean difference | 3.4 ± 3.2 | 8.5 ± 3.4 | 3.9 ± 7.2 | 14.6 ± 16.6 | 16.04 ± 3.8 |
| | NS | NS | NS | NS | < 0.01 |

[†]Determined by paired t test

CBFI ml/min 100 g LV =
-1300 + 5.16 SAP mm Hg - 0.016 SAP mm Hg

or SAP within 40 to 100 mm Hg the relationship appears linear and the predictive equation is

CBFI ml/min 100 g LV =
-702 + 3.03 SAP mm Hg $r = 0.99$ $p < 0.001$

Before coronary occlusion control LV functional reserve capacity estimates assessed by increasing aortic root pressure did not differ significantly among the five groups by analysis of variance (Fig 4). For all 25 animals the average

SAP at which the LAF attained 12 mm Hg prior to coronary occlusion was 130.4 ± 6.2 mm Hg. After 30 minutes of coronary occlusion in the four groups in which the left anterior interventricular coronary artery was ligated LAF of 12 mm Hg was attained during LV testing at a SAP level which was significantly lower than control. However the magnitude of this reduction in all four groups was similar by analysis of variance averaging 41.9 ± 6.2 mm Hg ($p < 0.001$) (Fig 4). In the sham group the results of the control and post sham occlusion did not differ.

dogs^{17, 22} Nakano²³ reported findings similar to ours in anesthetized dogs but the uncontrolled cardiac output in that study decreased drastically as a result of tachycardia. It should be stated however that in preparations with fixed cardiac output stroke volume bears an inverse relationship to HR and according to previous findings from this laboratory the workload imposed on the LV as judged by MVO_2 measurements is about one fifth of that imposed with HR increases at constant stroke volume.²⁴ It is therefore conceivable that different results in conscious dogs may at least in part reflect changes in cardiac output during rapid pacing.

With the assumption that loss of LV functional reserve capacity bears a directional although not necessarily linear relationship to the functional loss of myocardium the results of this study clearly indicate that systemic arterial pressure setting does not affect the extent of loss of functioning myocardium following coronary artery occlusion. Previous studies using electrophysiological or enzymatic correlates supported mutually opposing views.⁶ Recently Wyatt and co-workers⁴ in preparations with left anterior descending stenosis suggested that increasing afterload may have beneficial effects on myocardial metabolism but detrimental effects on ventricular function concluding that ischemic injury may be reduced by increasing arterial pressure but at the expense of LV function. Obviously results are bound to vary first according to the degree of stenosis which determines maximal coronary blood flow second according to the level and increment of arterial pressure which determine coronary blood flow and LV work and third according to the oxygenation of arterial blood. Our data (Figs 2 and 3) may provide some insight on the effect of systemic arterial pressure changes on the balance of myocardial O₂ supply and demand. Arterial pressure bears a linear relationship to MVO_2 but curvilinear near to CBF so that for pressure levels above 100 mm Hg the ratio of O₂ supply over demand becomes progressively less favorable. The average slope of MVO_2 increase in response to systemic arterial pressure increments is 0.163 ml O₂ per mm Hg. On the other hand for normal blood O₂ carrying capacity of 20 vol % O₂ supply within the 40 to 100 mm Hg pressure range is about three times steeper but above 100 mm Hg tends to plateau towards the MVO_2 slope. Obviously

in the presence of coronary stenotic lesion or lower O₂ carrying capacity the O₂ curve will be depressed accordingly. To indicate that an optimal relationship of O₂ to demand relationship occurs at about 100 mm Hg increase above as well as decrease below may have a potentially detrimental effect.

The reduction of tolerance to tachycardia following coronary occlusion did not differ between groups with different SAP setting. However the trend toward negative correlation of mean tolerated HR with SAP setting, especially at small values, may warrant further investigation both tachycardia²⁵ as well as ischemia result in incomplete myocardial relaxation.

The criteria of heart rate and arterial pressure used in this experimental study for estimating functional reserve capacity represent the variables which correlate by which survival and degree of injury are ultimately determined. Although the effects may differ it appears according to the results of this study that systemic arterial pressure setting at the early state of myocardial infarction is not an important determinant of functional and probably anatomical loss of myocardium. However since mean arterial pressure levels of about 100 mm Hg afford the best O₂ supply to demand ratio, this pressure level may be optimal for myocardial perfusion.

Summary

The effect of mean systemic arterial pressure (SAP) on myocardial O₂ consumption, coronary blood flow (CBF) and the left ventricular (LV) reserve capacity following coronary artery occlusion was studied in open chest pentobarbital anesthetized dogs with fixed cardiac output and controlled heart rate (HR) and SAP. In all animals baseline CBF and SAP were obtained and LV reserve capacity was determined by identifying the HR level which raised mean left atrial pressure to 100 mm Hg. After uniform placement of a coronary snare the dogs were randomized into equal groups and SAP was set at 40, 60, 80, 100 and 130 mm Hg. MVO_2 and CBF were redetermined and the coronary artery was ligated in all except one group (70 mm Hg) served as sham control. Thirty minutes after coronary occlusion MVO_2 , CBF and LV reserve capacity were determined again. Pressure

The basic assumption in this study is that normally LV functional reserve capacity is a measure of maximal functioning of all LV segments. Therefore loss of functional contribution of any of the segments would be reflected as a reduction of the total LV functional reserve. Previous work supports this rationale although not necessarily in the sense of a simple mathematical relationship.³⁻⁵

While only one complete sham group for the 70 mm Hg pressure setting was provided in this study other sham experiments performed at both the 70 and the 130 mm Hg pressure settings showed that pressure setting did not modify the estimates of LV functional reserve capacity before or after sham coronary artery occlusions. Since the pressure setting alone did not appear to have an independent effect on LV functional reserve capacity estimates the observed decrements after coronary artery occlusion were attributed exclusively to the functional loss of myocardium. Several aspects in the design of this study were different from those of previous studies,⁶⁻¹⁰ and might have contributed to different results: (1) complete coronary occlusion instead of stenosis was utilized; (2) left ventricular output was kept constant rather than allowed to vary in response to rate and pressure increases; (3) the arterial bypass extracorporeal circuit was probably stiffer than the normal arterial tree thereby a higher actual workload to the left ventricle may have been imposed for comparable mean arterial pressure settings.

Discussion of results The grossly estimated size of non perfused LV myocardium resulting from the coronary artery occlusion was substantial but uniform among groups. This may reflect uniformity of occlusion successful randomization but also to some extent the constancy of the controlled variables. Accordingly differences in LV functional reserve capacity among groups could not be attributed to non uniformity of coronary artery occlusion.

Previous work from this laboratory indicated that left ventricular efficiency does not change after coronary artery ligations which result in a wide range of sizes of ischemic myocardium.³ In this study constancy of MVO₂ before and after coronary ligation in each group with different systemic arterial pressure setting implies that efficiency of the intact myocardium also remains constant at different levels of LV workload. The

MVO₂ constancy is also indicative of the stability of preparations following coronary occlusion. Control MVO₂I values in the sham group were somewhat but not significantly lower than those of the experimental group operated at 70 mm Hg therefore values after sham coronary occlusion appeared higher than sham control.

The linear relationship of MVO₂I versus mean systemic arterial pressure setting (Fig. 2) was similar before and after coronary occlusion affecting up to 27% of LV mass. This further supports the notion that total left ventricular O₂ consumption is proportional to workload and independent of relative size of intact or ischemic myocardium.¹¹ Similar findings supporting the independence of total left ventricular O₂ consumption from the perfusion or oxygenation conditions of the myocardium were previously reported in preparations in which MVO₂I requirements were modified by means of heart rate changes before and after coronary occlusion.¹²

These findings indicate that for similar workload the reserve capacity of the myocardium is able to compensate for the functional loss of ischemic myocardium without change in O₂ cost. In other words left ventricular efficiency remains unchanged at all levels of function although the work per gram of functioning myocardium varies. On this basis the extent of functional loss of myocardium cannot be assessed by MVO₂ measurements as long as the loss is compensated by the functional reserve of the intact part. Left ventricular decompensation obviously will occur when the capacity of the intact part to consume O₂ and produce energy is exhausted. It follows logically that the larger the size of the remaining intact part the higher the energy demands the ventricle can handle before decompensation. Conversely the larger the size of functionally lost tissue the lower the tolerance to increased demands. However because of the possibility that the functionally lost tissue not only ceases contributing but may actually dissipate energy larger infarcts may impinge upon LV functional reserve capacity out of proportion to their size.

During the control testing of LV functional reserve capacity LAP of 12 mm Hg was attained at the rather low mean systemic arterial pressure level of 130 ± 6.8 mm Hg. This level however is in accord with previous reports.^{3,5} In regard to heart rate response previous studies reported a lower tolerance of heart rate in intact conscious

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IMPORTANT INFORMATION FOR AUTHORS

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perfused myocardium did not differ among groups ($27.6 \pm 1\%$) MVO, bore a linear relationship to \overline{SAP} setting whereas CBF bore a curvilinear relationship. Coronary occlusion did not modify these relationships. Significant but similar decreases in tolerated HR ($23.1 \pm 4.7 \text{ min}^{-1}$) and \overline{SAP} ($41.9 \pm 6.2 \text{ mm Hg}$) from control values were observed in all four groups regardless of \overline{SAP} setting.

We concluded that the impact of coronary occlusion on MVO, CBF, the loss of functional reserve capacity, and possibly the extent of ischemic injury of the left ventricle is not modified by afterload changes. However, optimal O_2 supply to demand ratio appears at \overline{SAP} of about 60 mm Hg.

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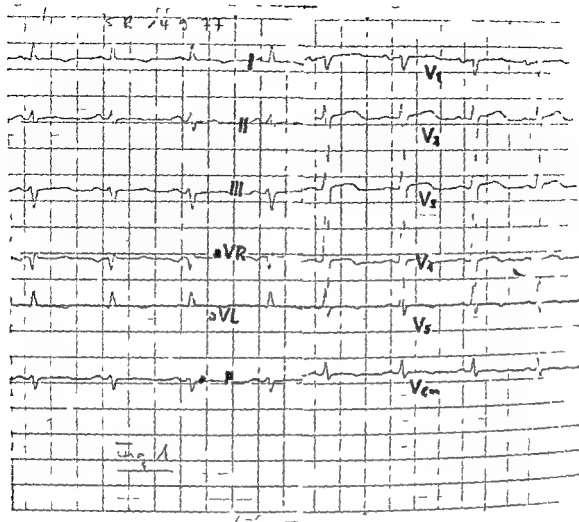


Fig 1 ECG on admission (see text)

dia (104/minute) a distinct pretibial edema enlargement of the heart on percussion splitting of the second heart sound and a soft systolic murmur at the apex on auscultation. The blood pressure was 140/80 mm Hg and the jugular venous pressure was not raised.

The electrocardiogram (Fig 1) showed a sinus tachycardia marked left axis deviation (greater than -45 degrees) resembling a left anterior hemiblock, minimally elevated convex ST segments terminally negative T waves in Leads I, II, aVL, and V. On x-ray (Fig 2) there was a cardiomegaly involving all chambers. The heart volume measured by the method of Muschoff and Reindell was 1030 ml or 15.8 ml/kg weight. In addition there were moderate signs of pulmonary congestion. The echocardiogram showed enlargement of the left ventricle with diminution of left posterior wall motion. There was no pericardial fluid.

The results of the laboratory studies are summarized below. Erythrocyte sedimentation rate was 103 mm in the first hour, white cell count was 200/mm³, plasma thyroxine was 7.1 μ g/l, plasma triiodothyronine was 104 μ g/l, antistreptolysin titre was below 200 IU, rheumatoid factor was negative, antistreptolysin B reaction 50 IU/ml, antistreptodornase B was 1.50, antihyaluronidase was 1 < 0.00, anti NADase was 1 < 50, antistaphylolysin reaction was 10 U/ml, and CRP was

negative. Titers for influenza A, influenza B, parvovirus, Epstein Bar virus, and Q fever were negative. No leucocytosis was observed. Antinuclear antibodies were not detected.

During the course of the disease (Table 1) complement fixing antibody titers rose from 1 < 16 (one week after onset of symptoms) to 1:256 (three weeks after onset). Cytomegalovirus (CMV) was isolated from the urine taken 14 days after onset of symptoms. Specific IgM antibodies were detected in the first serum specimen (first week titer 1:1024) and declined to the end of the third week (1:64).

The technique for the detection of IgM antibodies has been described in detail elsewhere¹⁰; the indirect immunofluorescence method was employed, using CMV infected human fibroblasts as a source of antigen and fluorescein-labeled globulin fraction against human μ -chain (donor rabbit origin).

For the detection of complement fixing antibodies¹¹ extracted antigen (Behring Werke, Marburg, Germany) was used. Virus isolation was carried out on human cells.

After three weeks bed rest the signs of heart failure disappeared. On discharge the electrocardiogram was normal (Fig 3) and the heart volume by echocardiography decreased to 710 ml, or 10.6 ml/kg, and was 14.5% of normal.

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Case reports

Cytomegalovirus myocarditis

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Cytomegalovirus infection is extremely frequent. However clinical manifestations are rare. Thus in Western Europe and in the USA 50 to 60% of adults^{1,2} in Great Britain about 55%^{3,4} and in Sweden 90 to 100% of persons over the age of 65.⁵ Low evidence of past infection. There was an infection rate in the newborn of 33% to 75% which decreased to 29% during the first year and in adults an incidence of 35%⁶ was observed. In Freiburg (W. Germany) the infection rate in the first six months of infancy was 20% to 30%.⁷ This incidence did not change in subsequent childhood until the period between 15 and 30 years when there was a second increase of the incidence to 7% to 70%. It is likely that after a subclinical infection the mother transfers the cytomegalovirus to the fetus^{8,9} which may lead to intrauterine death^{10,11} or prenatal infection with cerebral or visceral injuries.^{12,13} The perinatal and early postnatal infections are not distinctly separable from the visceral form of the prenatal infection. The infection of the older child and adult are acquired illnesses. Frequently a benign pathosis^{14,15} is observed but evidence of further systemic involvement such as heterophilic gammae infectious mononucleosis^{16,17} or polyneuritis of the Guillain Barre type and Fisher syndrome^{18,19} autoimmune hemolytic anemia²⁰ splenomegalies²¹ anorexia and ulcers²² but also inflammation of the lungs kidneys adrenals the vagina and other organs^{23,24} have been reported.

Table 1 Virological dates in the course of the disease

| | 1 week after onset | 14 days after onset | 3 weeks after onset |
|---------------------------------|-----------------------|------------------------|------------------------|
| Complement fixing antibodies | 1/16 | neg | 1/256 |
| IgM antibodies | 1/1024 | neg | 1/64 |
| CMV from urine | — | + | — |

neg = negative

Observations of alterations of the heart in cytomegalovirus infection are comparatively rare.^{25,26} Wilson Morris and Rees described a female patient, aged 60 years with a significant rise in cytomegalovirus complement fixing antibody who became increasingly breathless and had repeated attacks of paroxysmal dyspnea after a head cold which progressed to dry cough and wheezing. On clinical examination she was obviously ill febrile (38.2° C) and dyspneic at rest. The jugular venous pressure was raised 5 cm above the sternal angle. There was gallop rhythm with pansystolic and mid diastolic murmurs at the apex and also fine rales at both lung bases. The electrocardiogram showed sinus tachycardia left bundle branch block and left ventricular hypertrophy. The chest x ray demonstrated cardiomegaly and pulmonary congestion.

Because cytomegalovirus myocarditis is rare we felt justified in reporting a comparable patient of our own.

Case report

One week before his admission to hospital, a previously healthy man aged 31 years, became progressively breathless on effort, needing to rest after going up one flight of stairs. Moreover he noticed swelling of his ankles and legs. He had nocturia three times each night.

Previously no cardiac abnormalities had been detected. The patient presented with low grade fever (37.5° C) a tachycardia

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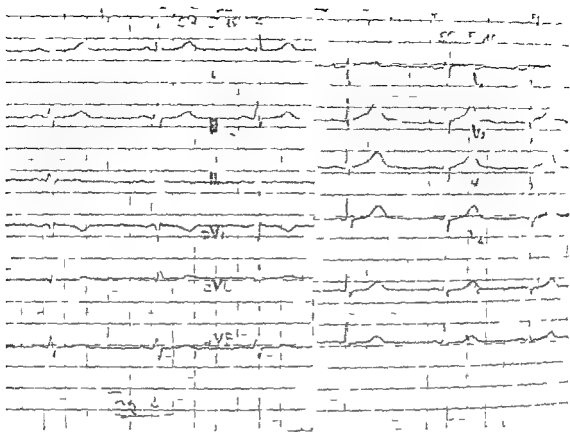


Fig 3 ECG on discharge (see text)

complement fixing antibodies from $1 < 8$ to $1 > 64$. At necropsy the heart was enlarged and weighed 515 g. The microscopic examination showed foci with lymphocytic infiltration and focal fibrosis. No inclusion bodies could be seen. The pericardial sac contained 180 ml of hemorrhagic fluid so that the question arises whether there was a hemorrhagic tamponade of the heart following the heparin treatment of the coagulopathy.

The role of drug treatment of cytomegalovirus infections is unclear. Idoxuridine has been effective in infections with the herpes virus^{1,22} to which group of viruses the cytomegalovirus also belongs. This drug was also used in cytomegalovirus infection with success defined as clinical improvement as well as lowering of the urine content of viruses.⁹ Floxuridine and 5-fluorodeoxyuridine seemed to have a favorable effect on patients with cytomegalovirus pneumonia and seemed to shorten the clinical course if they were also combined with prednisolone.¹⁰ The successful use in generalized herpes infection of cytosine arabinoside hydrochloride²³ a newer antiviral

agent led Wilson Morris and Rees⁴ to its application in their patient with cytomegalovirus myocarditis but only a fall in the JVP venous pressure accompanied by a fall in viral titer were observed. Their patient has remained symptom free on a strict regimen, persisting gallop rhythm, mitral regurgitant murmur, left bundle branch block, and cardiomegaly.

In view of the many potential toxic side effects of the above mentioned antiviral drugs, it probably should be used with restraint and conservative means of therapy applied to all viral forms of myocarditis such as prolonged rest, digitalis, diuretics etc. should be seriously considered for these patients.

Prophylaxis by the development of vaccination techniques is now being investigated but the clinical application of these techniques is justified.¹

Summary

A male patient aged 31 years, with a cytomegalovirus (CMV) myocarditis is described.¹

normal limits (Fig 4). Also the echocardiogram showed no pathologic findings. The ESR normalized to 7 mm. There have been several reexaminations of the patient to the date of reporting, none of which have shown signs of recurrence.

Discussion

The diagnosis of cytomegalovirus infection has been improved in recent years because of the development of laboratory methods for determination of different cytomegalovirus immunoglobulins (IgG, IgM, IgA) by immunofluorescence^{49, 50} therefore the diagnosis of a fresh infection is not dependent on the laborious virus isolation. The presence of virus specific IgM antibodies especially seems to be very helpful for diagnosis of recent CMV infection. In our case reported here we were able to detect

1. a cytomegalovirus IgM antibody titer of > 64

2. a fourfold increase in the titer of complement fixing antibodies and

3. virus isolated from urine

thus a recent CMV infection is supported by several diagnostic parameters

In the older child and in the adult the appearance of IgM antibodies is a reliable sign of an active process^{50, 51} even if relatively low KBR titers of 1:16 are found.⁵ Usually the IgM antibodies will also be eliminated from the serum several months after the infection⁵ and therefore still have a great diagnostic significance.

The IgG antibodies however may be demonstrable for years⁵² and therefore serve as a sign of past infection. In the isolation of the virus from urine care must be taken to avoid rapid inactivation of the virus at room temperature and therefore the specimen must be quickly transported to the virology laboratory.

Cytomegalovirus infection is frequently associated with other severe conditions such as leukemia, malignant lymphoma, lymphogranuloma, myocardial infarction, pneumonia, fungus infection, liver abscess, toxoplasmosis, sepsis, miliary tuberculosis or other debilitating conditions.^{53, 54, 55} or appears after cytostatic, immunosuppressive and corticosteroid drugs, transplantation of the kidney, blood transfusion, open heart surgery.^{1, 10, 13, 14, 17, 24}

It should be emphasized that it also may occur in previously healthy and unmedicated persons.^{10, 22, 23, 25, 35}

The slightly elevated ST segments resemble the electrocardiographic changes seen in pericarditis.

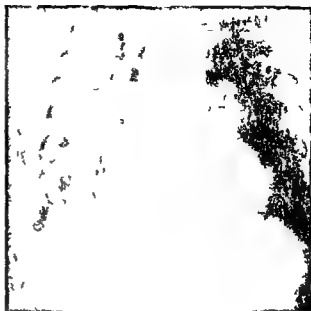


Fig 2. Chest x ray on admission showing cardiomegaly and pulmonary congestion.

combined with myocarditis. This interpretation is not supported by the clinical findings as our patient did not experience pericardial pain and a pericardial friction rub was never elicited.

The prognosis of cytomegalovirus myocarditis is not universally agreed upon. Thus Sterner and colleagues⁵ in two of 17 patients aged between 6 and 71 years with serologic and virologic evidence of cytomegalovirus infection and Klemola and co-workers¹ in a female patient aged 18 years and in a second female patient aged 66 years and also in a male patient aged 19 years with serologically verified cytomegalovirus mononucleosis saw transient flattening and inversion of T waves in the electrocardiogram. Our patient with signs of heart failure, distinct alterations in the electrocardiogram and cardiomegaly on x ray recovered completely only after prolonged bedrest.

In the patient of Wilson, Morris and Rees¹ there was a partial remission. At the time of writing their paper the patient had survived with cardiac residuals such as alterations in electrocardiogram and cardiomegaly on x ray. The 14-year-old boy described by Tuula and Lemikki⁷ died with signs of cardiogenic shock. The main clinical manifestations were carditis, hepatitis and consumption coagulopathy. Myocardial insufficiency developed and worsened in spite of digitalis treatment. There was a seroconversion in

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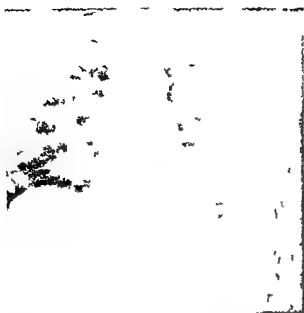


Fig. 4. Chest x ray on discharge (see text)

showed a high IgM antibody titer for cytomegalovirus infection of 1:1024 and a rise of the titer of complement fixing antibody from 1:16 to 1:256. CMV could be isolated from the urine. Investigations for other etiological factors were negative and we assumed a connection between the cytomegalovirus infection and the myocardial involvement.

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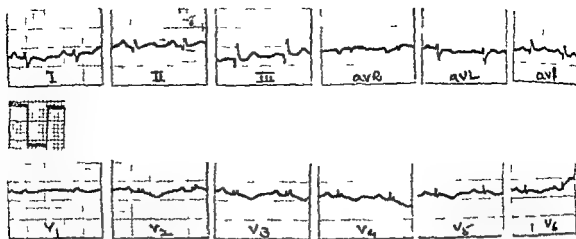


Fig 2 Electrocardiogram of the same patient as in Fig 1 showing frontal plane QRS axis of +120 degrees, generalized low voltage QRS complexes with non specific ST T wave changes

Table 1 Hemodynamic data

| Chamber | Pressure | Oxygen saturation |
|------------------|-----------------------|-------------------|
| Right atrium | a = 12 v = 12 (10) | |
| Right ventricle | 12/7 5 10 | |
| Pulmonary artery | 12/7 (10) | 52% |
| Left ventricle | 85/0 7 | |
| Aorta | 80/60 (72) | 100% |

Pressure tracing identical (see Fig 3)

Neck veins were not prominent. There was no appreciable precordial impulse. The heart sounds were muffled in intensity and there were no murmurs or gallop sounds. Lungs were clear to auscultation. A chest roentgenogram (Fig 1) showed considerable cardiomegaly, the cardiac silhouette occupying almost the whole of the hemithorax. Pulmonary vascular markings were unremarkable. The electrocardiogram (Fig 2) revealed normal P waves, a QRS frontal plane axis of +120 degrees, generalized low voltage complexes with non specific ST T changes, a precordial tracing showed q or complex of very low amplitude in Lead V₁ and very tiny complexes from Leads V₂ to V₆. Cardiac catheterization revealed the characteristic finding of identical right atrial, right ventricular and pulmonary artery pressure tracings (Fig 3). A simultaneous electrode catheter intracardiac tracing for diagnosis of Ebstein's disease was of no help, since pressure tracings of the right atrium and right ventricle were similar. The left heart study revealed normal pressures (Table 1). A right atrial cineangiogram showed a normally located tricuspid valve, enormous dilation of the right ventricle which formed most of the cardiac contour with very scanty trabeculae (Fig 4). Pulmonary artery filling was delayed and clearance of the dye from the right ventricle was very slow, a left ventricular cineangiogram was normal.

These hemodynamic and angiographic features suggested the diagnosis of parchment right ventricle with normal tricuspid valve (Uhl's anomaly). In view of persistent refractory

right heart failure and the failure to thrive the child was subjected to superior vena cava right pulmonary artery anastomosis (Glenn's operation). At surgery the right atrium was found to be hypertrophied and enlarged. The right ventricle was tremendously enlarged and very thin. The child was well for 3 hours after operation when sinus bradycardia developed to 20/minute with intermittent junctional escape beats noted. This was accompanied by profound hypotension. Central atropine was of no help. Transvenous right ventricular pacing was tried from different sites but capture could not be obtained and before left ventricular epicardial pacing could be tried the child died.

Postmortem examination. The autopsy was limited to the heart and lungs. The lungs showed chronic passive hyperemia and small peripheral pulmonary emboli.

Gross examination (Fig 5). The heart was enlarged; combined weight of heart and both lungs was 250 g. The right atrium was hypertrophied and enlarged. The external surface showed a postmortem thrombus on the right atrial free wall. There was a patent shunt between the superior vena cava and the right pulmonary artery with a purse-string suture at the junction of the right atrium and superior vena cava. The tricuspid orifice was dilated but the cusps and apparatus were normal. The right ventricle was enormously enlarged with areas of saccululation. The myocardium could be recognized in the anterior surface and outflow tract of the right ventricle. Scanty myocardium with trabeculae could be identified in portions of the inflow tract of the right ventricle and the thickness of the wall in these areas varied from less than 1 mm to 3 mm. The endocardium was considerably thickened and appeared whitened in the inflow and outflow tract. The pulmonary orifice diameter was normal but at the site of the pulmonary valve there were rudimentary cusps which could be identified. These were very thin and delicate. The pulmonary trunk and branches were normal.

The left atrium, left ventricle, mitral and aortic valves were normal. The coronary arteries and its branches were normal.

Microscopy

RIGHT ATRIUM. The endocardium of the atrium was normal.

Uhl's anomaly with rudimentary pulmonary valve leaflets: A clinical, hemodynamic, angiographic and pathologic study

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Uhl's anomaly is a rare condition characterized by partial or complete absence of the myocardium of the right ventricle and its replacement by fibroelastic and adipose tissue in the presence of a normal tricuspid valve.^{1,2} Although the original description was in a heart with normal aortic valve, pulmonary atresia, pulmonary stenosis and atrial septal defect have been reported in association with Uhl's anomaly.³ The antemortem diagnosis of this condition is rare and only three cases have been described.³⁻⁵ The present report is the fourth case of Uhl's anomaly diagnosed by characteristic hemodynamic and angiographic features. The patient died in the immediate postoperative period following Glenn's operation. Autopsy revealed partial parchment right ventricle, normal tricuspid valve and rudimentary pulmonary valve. This association has not been reported previously.

Clinical report

V.K., a 4-year-old male child, was the product of a full term normal delivery (birth weight, 2.5 kg). When the infant was 6 months old his mother noticed swelling of the body besides his failure to grow well. The child was admitted to one of the city hospitals where examination revealed facial puffiness, pitting edema, muffled heart sounds, and no cardiac murmur. The liver was enlarged 5 cm. below the right costal margin. In view of radiological evidence of gross cardiomegaly with clear lung fields, a pericardial tap was done but no fluid could be



Fig 1. Roentgenogram of the chest of a 4-year-old male patient with Uhl's anomaly showing enormous cardiomegaly and clear lung fields.

aspirated. The child was started on digitalis and diuretics, the edema subsided and hepatomegaly regressed, but there was no change in the cardiac size. Despite regular treatment, the congestive heart failure continued to progress for 3 years and the child was admitted to G.B. Pant Hospital, New Delhi, in August 1977. Milestones of the child were delayed. There was no history of dyspnea, cyanosis, anoxic spells, or repeated chest infections.

Physical examination revealed an ill-looking child (height 96 cm., weight 10 kg.) with generalized edema. There was no central cyanosis or clubbing of the digits. Peripheral pulses were regular but of low volume. Blood pressure was 90/70 mm Hg. The liver edge was 6 cm. below the right costal margin.

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Fig 6 Autopsy specimen of the heart with the right ventricle opened up showing the trabecular pattern in the right ventricular inflow tract and the parchment like body and outflow. Note the rudimentary pulmonary valve leaflets (arrow)

graphic findings in this condition are similar pulse contours in the right atrium, right ventricle and pulmonary artery, elevated right ventricular end diastolic pressure and pulmonary artery diastolic pressure due to a prominent a wave.³ The right ventricle thus functions as a reservoir for venous blood. Differentiation from Ebstein's disease is possible on angiocardiology which reveals a normally located tricuspid valve in Uhl's disease with enormous right ventricular dilatation and with absent or scanty trabeculae. Pulmonary artery filling is delayed. Scanty delayed filling of the left heart can be seen in the levophase of the right sided angiogram.^{3,4} The echocardiographic findings of diastolic pulmonary valve opening, increased right ventricular dimensions, delayed tricuspid closure and abnormality of the mitral valve have been reported in an isolated case report.⁵ The absence of a diastolic pulmonary regurgitation murmur and the normal size of the main pulmonary artery and its branches signifies that there was no appreciable pulmonary regurgitation in the present case despite rudimentary pulmonary valve leaflets.

The prognosis in these cases is very poor. Gasul and colleagues have suggested superior vena cava right pulmonary artery anastomosis as a surgical remedy for this condition and have reported a case with a successful outcome.

The postoperative rhythm disturbance seen in

our patient seems to have arisen due to supra-ventricular trauma or edema in the region of the sinoatrial node by the purse string suture. The failure of right ventricular endocardial pacing which we encountered has also been recently experienced by Bharati and associates⁶ in a case of Uhl's anomaly which presented with a complete bundle branch block and narrow QRS complexes of recent onset. The conduction system examination in the case revealed total destruction of both bundle branches.

Summary

An acyanotic 4 year old male child who failed to thrive presented with signs of persistent right heart failure and no cardiac murmurs. There was no radiologic evidence of gross cardiomegaly with unremarkable lung fields. Cardiac catheterization and cineangiographic features helped in arriving at the diagnosis of parchment right ventricle with normal tricuspid valve (Uhl's anomaly) a condition seldom diagnosed during life. The patient was subjected to surgery and Glenn's operation was performed following which he died of a low output state and bradyarrhythmia. Autopsy revealed partial parchment right ventricle with rudimentary pulmonary valve leaflets, a combination not described previously.

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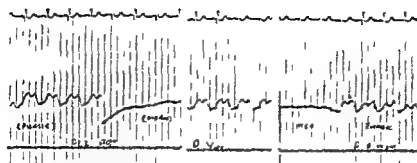


Fig 3 Pressure tracings from the pulmonary artery (PULM. ART.), right ventricle (RT VENTR.), and right atrium (RT ATRIUM) showing identical pressure pulse tracings.

the myocardium showed an increase in the elastic tissue. The muscle fibers showed edema, vacuolization, and nuclear hypertrophy.

RIGHT VENTRICLE. Microsections from the anterior surface and outflow tract showed complete absence of muscle with only adipose and fibrous tissue between the endocardium and epicardium. In areas of inflow where scanty muscle fibers were present, the muscle fibers showed vacuolization and regenerative changes in the cytoplasm. The nuclei were bizarre in shape and there were no inflammatory cells.

PULMONARY VALVE. The pulmonary valve cusps were represented by small vestiges of fibrous tissue with only occasional areas showing endothelial lining.

The left atrium, left ventricle, aortic valve, mitral valve, aorta, and pulmonary trunk were normal.

Discussion

Uhl's disease is a condition with partial or complete absence of the myocardium in the right ventricle and its replacement by fibroelastic and adipose tissue in the presence of a normal tricuspid valve.¹⁻³ In the literature, others have included parchment right ventricle with atrial septal defect, pulmonic stenosis, and pulmonary atresia.¹⁴ The association of Uhl's anomaly with rudimentary or absent pulmonary valve has not been reported so far. The differential diagnosis of Uhl's anomaly includes conditions like Ebstein's anomaly, pericardial effusion, primary endocardial fibroelastosis, glycogen storage disease of the heart, and anomalous origin of the left coronary artery from the pulmonary artery.

The patients with this disorder present in infancy with congestive heart failure without dyspnea unless there is an associated left-sided involvement like endocardial fibroelastosis. Occasionally Uhl's disease has been reported as an incidental autopsy finding.

Radiological examination shows a considerable



Fig 4 Right atrial cineangiogram showing normally located tricuspid valve (arrow) and enormously dilated right ventricle forming most of the cardiac silhouette with absent trabecular pattern.

cardiomegaly even occupying the whole of the left hemithorax.¹⁻³ The electrocardiogram shows generalized low voltage QRS complexes with or without evidence of P pulmonale.¹⁻³ The great majority of cases reported in the literature were diagnosed at autopsy.¹⁻³ Most of the cases described were erroneously diagnosed as Ebstein's anomaly. One of the cases reported in the literature was erroneously diagnosed as mediastinal tumor; necropsy established the correct diagnosis. This anomaly has been diagnosed antemortem only on three previous occasions.¹⁻³ The typical hemodynamic and angio-

Dissimilar atrial rhythms A patient with triple right atrial rhythm

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Partial intra atrial block seems to be a frequent electrocardiographic finding. Conversely dissimilar atrial rhythms due to a higher degree of intra or inter atrial block have been reported infrequently after the first clinical description. However since the electrical activity of one atrium or of a segment of the atria may not be registered by the conventional electrocardiogram (ECG) it seems reasonable to assume that the true incidence of these arrhythmias may have been underestimated.

Recently several forms of dissimilar atrial rhythms were only detected by multiple intracardiac electrocardiographic tracings.¹⁻³ These forms include electrical atrial standstill with flutter or tachycardia in another segment of the atria. Persistent standstill of only one atrium in the absence of other heart disease has also been described.⁴

We report here an unusual case of A V block and atrial fibrillation in the surface ECG in which the electrophysiological study demonstrated three areas in the right atrium each of them with different electrophysiological properties.

Case report

Clinical features A 44-year-old man followed up in the Outpatient Department because of complete A V block was

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referred to our laboratory for intracardiac study preceding 11 months he only complained of dizziness, was no past history suggestive of heart disease and was administered. On examination he exhibited a rate of 40/minute. Neither "a" waves nor catheters were seen on the jugular veins. The blood pressure was 100 mm. Hg. A chest x ray film revealed slight cardiac enlargement. ECG showed atrial fibrillation, complete A V narrow QRS complexes, and a pattern of second degree bundle branch block. The "f" waves reflected very irregularly and could be seen only in some leads (Fig. 1A).

Electrophysiologic study After obtaining consent a catheter was percutaneously introduced through the femoral vein, and was placed across the septal leaflet of the tricuspid valve for bundle of His recording, and moved to various sites in the right atrium. Another catheter was introduced through an antecubital vein for pacing or recording electrograms from various sites in the right atrium, from the coronary sinus, and from the ventricle. An additional bipolar catheter was placed in the esophagus for recording left atrial activity. Filtered (40 to 400 Hz) intracavitary right heart electrograms were recorded simultaneously with surface leads. The recording system (Electronics for Medicine DR 8 photographic recorder) was set at speeds of 100 and 200 mm./sec. Electrical stimuli (1 msec. duration) were introduced by a Hewlett Model 7604 A pacemaker.

Results No atrial electrical activity could be recorded with the catheter positioned near the sinus node (Fig. 1B) and at different levels of the anterolateral wall of the right atrium. Catheter 2, placed at the highest point of the interatrial septum, registered coarse fibrillatory waves of coarse atrial fibrillation (Fig. 1C). Catheter 3, located at the lower portion of the septum and RA, showed the same features as catheter 2. However catheter 1, now placed at the coronary sinus, registered an irregular atrial activity (Fig. 1D) at a rate of 40/minute (RA). In other recording (Fig. 1E), catheter 1 positioned at the atrial zone adjacent to the tricuspid valve and fibrillatory waves were registered. Catheter 2, located between both areas in which fibrillatory waves were obtained. The recordings of the irregular atrial activity showed irregular waves of very low amplitude with a rate of 40/minute. These waves coincided with the major deflections of RA. Ex-

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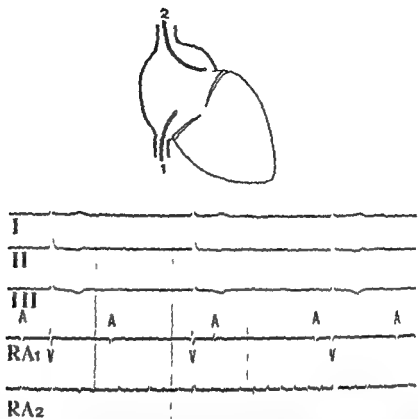


Fig 2 Catheter 1 is now placed at the coronary sinus area and its electrogram (RA) shows irregular atrial activity (A waves) with a rate of 50/minute. The electrogram registered by catheter 2 positioned at the lower portion of the interatrial septum (RA) shows similar findings to those seen in Fig 1. See text for discussion.

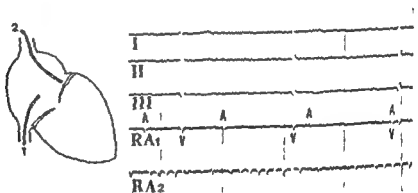


Fig 3 The fibrilloflutter waves recorded by catheter 2 located at the tricuspid area (RA) are larger than in Fig 1 and Fig 2. Catheter 1 is placed between areas in which fibrilloflutter waves and irregular atrial activity (A waves) are registered. The electrogram (RA) reflects irregular fibrilloflutter waves of very low amplitude with a rate of 450 per minute. These waves do not occur synchronously with the larger fibrilloflutter waves registered in RA. (See text.)

anterolateral wall supported by (1) no detectable atrial waves and (2) no response to atrial stimulation." Zone B: irregular and slow atrial activity evidenced by A waves with a rate of 50/minute with apparent entrance and exit block and Zone C: fibrilloflutter waves registered in the entire right surface of the interatrial septum and in the

area adjacent to the tricuspid valve. In Fig 1, catheter positioned between Zones B and C recorded small and irregular waves propagated from the latter. However, since waves occur at different times than those registered in Zone C and there is no regular sequence (e.g., Wenckebach periodicity) between

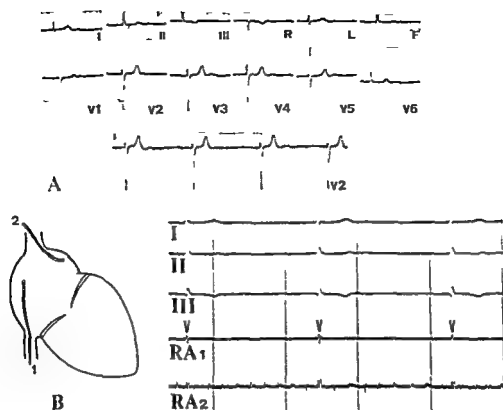


Fig 1 In this and in subsequent figures the diagram reflects the position of the catheters. RA and RA₂ are the electrograms registered with catheter 1 and catheter 2, respectively. A Standard 12 lead ECG and rhythm strip (V) showing complete A V block with narrow QRS complexes. Note the very low voltage of atrial deflections (f waves). B The upper electrogram (RA) reflects atrial standstill whereas the lower electrogram (RA₂) shows fibrillatory waves. V = ventricular deflections. Vertical time lines are 1 sec. apart. See text for details.

lation (S) with 10 to 15 mA, performed in the atrial standstill zone was not propagated, as can be seen in Fig 4A. Catheter 1 (RA) was located 1.5 to 2 cm. away from the pacing catheter (S). In Fig 4B the latter was positioned in the right ventricle. Ventricular endocardial stimulation (S) was not conducted to the coronary sinus area registered with catheter 1 (RA). The left atrial electrograms obtained by intracoronary sinus and atrioesophageal catheters reflected fibrillatory waves (not shown).

The electrophysiological study was repeated two weeks later and the results previously described were confirmed.

In the follow up period up to 7 months the surface ECG showed similar findings, and in spite of the fact that the patient remained asymptomatic a permanent pacemaker was indicated.

Discussion

The diagnostic criteria and differential diagnosis of most forms of dissimilar atrial rhythms have been well summarized by Chung. As can be deduced from the analysis of these data the scalar ECG gave sufficient information about the atrial events when the sinus rhythm coexisted with other dissociated regular atrial rhythms or when flutter or fibrillation in a segment of the

atria developed during sinus rhythm. Conversely in the other reported forms the diagnosis was only suspected or misinterpreted.

According to Wu and colleagues⁶ the electrocardiographic manifestations of an atrial rhythm are dependent upon (1) the atrial mass depolarized and (2) the vicinity of the recording electrodes to this atrial mass. Thus in most instances only with multiple intracavitary electrograms is it possible to demonstrate atrial events in patients with unclear forms of atrial arrhythmias.

In our patient the surface ECG showed complete A V block without detectable atrial activity in most leads. Only in amplified rhythm strips could a slight irregularity of the baseline be seen and the diagnosis of atrial fibrillation was established. However the possibility of an atrial standstill was considered. The intracardiac study demonstrated three areas in the right atrium each of them with different electrophysiological properties. Zone A: persistent atrial standstill in the

demonstrate atrial events in patients with atrial arrhythmias. They may be of important clinical significance given the large number of new antiarrhythmic drugs with very different electrophysiological effects recently introduced. On the other hand the clinical features of this and other recently reported cases¹⁻⁴ demonstrate that dissimilar atrial rhythms may be registered in several types of heart disease. In contrast earlier clinical studies suggested that atrial dissociation was almost always found in critically ill patients with intractable heart failure.

Summary

A patient with complete A-V block and atrial fibrillation was analyzed by multiple intra atrial electrograms. Three areas were recorded in the right atrium each of them with different electrophysiological properties: (1) persistent atrial standstill, (2) irregular atrial activity with a rate of 50/minute and (3) fibrilloflutter waves with a rate of 450/minute. The latter were also registered in the left atrium.

This case illustrates another form of dissimilar atrial rhythms and provides additional evidence of the importance of recording multiple electrograms from each atrium in the evaluation of the atrial events in atypical atrial arrhythmias.

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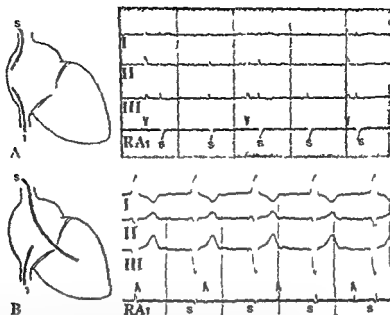


Fig 4 A Electrical stimulation performed in the atrial standstill zone (S) is not propagated (RA) Catheter 1 is located 1.5 cm away from the pacing catheter (S) B Ventricular endocardial stimulation is not conducted to the coronary sinus area recorded with catheter 1 (RA) See text

another independent atrial activity localized to a small area in the right atrium cannot be excluded. In the left atrium fibrilloflutter waves were also registered. His bundle electrograms were not identified in the two electrophysiological studies. It is possible that the fibrilloflutter waves which were coarser in the vicinity of the tricuspid area than in the upper portion of the interatrial septum (Fig 3) masked the His potentials.

Although the electrophysiological mechanism of atrial dissociation and other forms of dissimilar atrial rhythms have not yet been fully elucidated, the above mentioned studies with intra atrial recordings provide evidence supporting the existence of inter and intra atrial blocks. If an interatrial block is only partial, a first degree of interatrial block occurs with two components (right and left) of the P waves separated by an isoelectric period as in Case 1 of Wu and colleagues⁴ and in other reported cases with surface ECGs.¹ If a higher interatrial block is present, only some of the unilateral atrial depolarizations (right or left) are conducted to the other chamber and a second degree of interatrial block, with or without Wenckebach phenomenon, can be considered as in the cases reported by Zipes and DeJoseph.⁶ Finally, if the interatrial block is complete, a true atrial dissociation with two independent rhythms occurs. Experimental and clinical studies suggest Bachman's bundle as the

site of the block. However, in most cases of these so-called third-degree of interatrial block, the site of block appears to be located within the same atrium rather than between the two atrial chambers as in Case 2 reported by Wu and associates.

In our patient, the three dissimilar atrial rhythms were located in the right atrium. The limits of the three different areas were well demarcated as could be demonstrated by multiple and repeated positioning of the catheters during the two electrophysiological studies performed. These findings may be considered as evidence of the existence of two ectopic foci with complete exit and entrance blocks. Furthermore, the presence of a considerable area with atrial standstill presumably indicates an advanced degree of atrial disease. This suggests that atrial fibers may show nonhomogeneous refractoriness with multiple sites of partial or complete intra atrial blocks. However, on the same basis, it is also possible to assume the alternative explanation postulated by Zipes and DeJoseph,⁶ the slow atrial activity recorded in Zone B may be secondary to a constant filtering of the fibrillatory stimulus originating in Zone C and in the left atrium.

The results of this study as well as previous publications emphasize the importance of recording multiple electrograms from each atrium to

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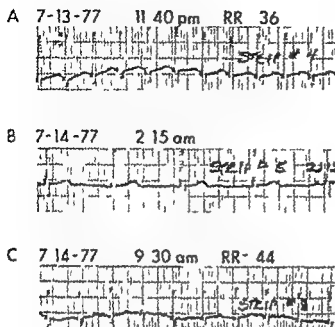


Fig 1 Holter monitor recording Patient No 1. Panel A was recorded during sleep and shows supraventricular tachycardia with a rate of 166 minute. Panel B was also recorded during sleep and shows sinus rhythm. Panel C was recorded in the early morning and shows supraventricular tachycardia at a rate of 136 minute. The patient was resting quietly at the time Panel C was recorded and experienced no symptoms.

and retrograde direction was assessed by fixed rate pacing and the extrastimulus technique (Fig 2) using stimulation to the right atrium, coronary sinus (left atrium) and right ventricle. The A-V induction system was normal and no tachyarrhythmias induced during the study.

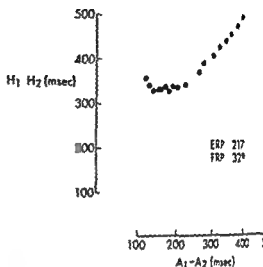
Electroencephalographic findings. The background rhythm of the EEG consisted of a well-developed and well modulated alpha rhythm at a frequency of 8 Hz. The major abnormality detected was repetitive epileptiform discharges consisting of both sharp and spike wave transients arising from the lateral aspect of the right mid and anterior temporal regions. These findings would provide the basis for a diagnosis of epilepsy of temporal lobe origin in symptomatic patients. No arrhythmic arrhythmias occurred during simultaneous monitoring of the EEG and electrocardiogram.

Clinical course. The patient was treated initially with phenytoin 100 mg three times daily but symptoms persisted. He then was treated with carbamazepine 400 mg twice a day. On this dose carbamazepine level (drawn 12 hours after the preceding dose) was 3.0 mg/ml. After one month of therapy, neurologic symptoms and all symptomatic arrhythmias had resolved. A 48 hr Holter monitor recording showed only sinus rhythm.

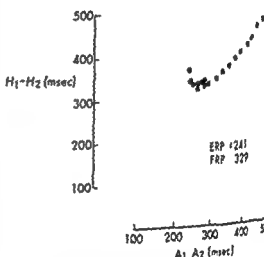
Clinical history

Patient No 2 (born) was a 13-year-old white male who was referred to Duke University in October 1976 for treatment of cardiac arrhythmias. His prenatal and perinatal

A RA PACING CL 500



B CS PACING CL 500



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Fig 2 Refractory periods of the atrioventricular node. Patient No 1. Panel A right atrial pacing. The upper curve is the effective refractory period, and the lower curve is the normal A-V refractory period. Panel B coronary sinus pacing. The curve is similar to the curve obtained during atrial pacing. Atrial refractoriness prevented estimation of the refractory periods of the A-V node during coronary sinus pacing. ERP = effective refractory period. FRP = functional refractory period.

history was unremarkable. His mother commented that as an infant he appeared to have a rapid heart rate but this was not recorded. At age 12 he had an episode of loss of consciousness. He was taken to a hospital emergency room where a diagnosis of atrial flutter was made. He was hospitalized. One month later he had a second episode of loss of consciousness. Both bradycardia and tachycardia were

Arrhythmogenic epilepsy: an hypothesis

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Durham N C

Spontaneous paroxysmal supraventricular tachycardia (PSVT) can almost always be reproduced in patients with this arrhythmia by programmed stimulation in the electrophysiology laboratory.¹ The arrhythmia may be caused by reentry within the atrioventricular (AV) node or reentry within the sinus node or reentry using an accessory A-V pathway.² We recently studied two patients who had multiple arrhythmias including PSVT. Electrophysiologic mechanisms for the arrhythmias could not be demonstrated by programmed stimulation in either patient. Both patients were found to have epileptiform abnormalities demonstrated by electroencephalogram (EEG). A primary neurologic abnormality was the probable cause for the arrhythmias in these patients.

Case reports

Patient No 1

Clinical history: Patient No 1 was a 21 year old college student when he was referred to Duke University in April

1978 to the Division of Cardiology and Neurology of the Department of Medicine, Duke University Medical Center, Durham, N.C. He was supported in part by Grant RR-30 from the General Clinical Research Centers Branch, Division of Health Resources, Bethesda, Md. Received for publication June 14, 1979. Accepted for publication in July 1979. Send correspondence to Edward L C Pritchett MD, Duke University Medical Center, Department of Medicine, Division of Cardiology, Durham, N.C. 27710.

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This work was done during Dr Gallagher's tenure as Established Investigator of the American Heart Association. Dr Gallagher is Associate Professor of Medicine, Division of Cardiology and Director of Clinical Electrophysiology Laboratory, Duke University Medical Center.

Table 1 Conduction intervals

| | Patient 1 | Patient 2 |
|------------------------------|--------------|---------------|
| Sinus cycle msec (beats/min) | 730 (82/min) | 465 (129/min) |
| PA interval (msec) | 40 | 20 |
| AH interval (msec) | 60 | 50 |
| HV interval (msec) | 40 | 45 |
| QRS morphology | normal | normal |

1978 for treatment of cardiac arrhythmias. His first recollection of symptoms suggestive of tachycardia occurred in October 1976. At that time he was bowling and experienced dizziness and dyspnea. A nurse was present and stated that his pulse was "very fast." The episode terminated abruptly after 30 minutes. Two weeks later he experienced palpitations, dyspnea, and nausea in a restaurant. Observers reported that he lost consciousness for approximately 10 minutes but was not incontinent and did not have tonic or clonic seizures. He awoke and returned home where his mother felt his pulse and noted that it was approximately 200 beats/minute. He continued to have two or three attacks of altered consciousness per month between October 1976 and July 1977. Some attacks were accompanied by palpitations; other similar episodes were not. In July 1977 a Holter monitor recording demonstrated two episodes of supraventricular tachycardia (Fig. 1) that caused no symptoms. During tachycardia the QRS morphology was normal. He was treated with digoxin, propranolol, quinidine and combinations of these drugs but none modified the frequency or severity of tachycardia or dizziness. He was referred for further evaluation and treatment.

The vital signs were normal and the cardiovascular and neurologic systems were normal by clinical examination. An electrocardiogram recorded at the time of admission was normal.

The patient had four hospital admissions between April and August 1978. During these hospitalizations he had continuous monitoring of his electrocardiogram in the Coronary Care Unit. Holter monitor recordings were also made. The dominant arrhythmia was sinus arrest with an ectopic atrial pacemaker at a rate slower than the sinus rate. The patient had no symptoms and no spontaneous tachycardias while in the hospital.

Results of electrophysiologic testing: Basic A-V conduction intervals are shown in Table 1. Sinus node recovery times were normal. The A-V conduction system in the antegrade

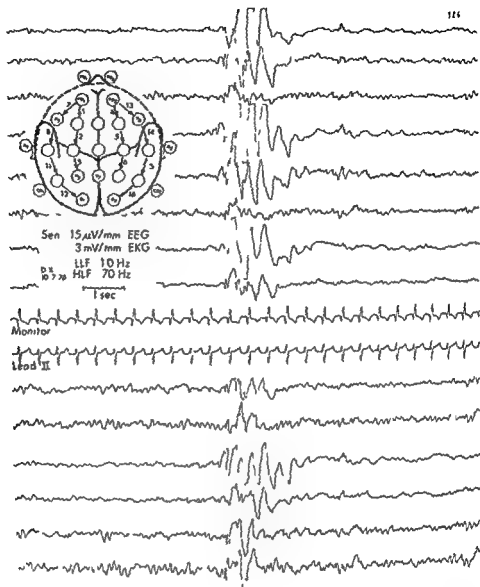


Fig 4 Epileptiform discharges on EEG on Patient No 2 Supraventricular tachycardia is present throughout the recording

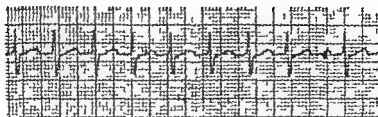
one case to drive a car) even though tachycardia persisted

Paroxysmal supraventricular tachycardia was a prominent arrhythmia recorded in both patients but three features of the arrhythmia were unusual. As noted above, PSVT rarely causes loss of consciousness. Also, common antiarrhythmic drugs failed to alter the frequency, duration or severity of attacks. In addition, no etiology could be found for the PSVT and other arrhythmias when electrophysiologic studies were done. This arrhythmia has been studied intensively with electrophysiologic techniques for several years. The etiology can be demonstrated by laboratory methods in approxi-

mately 90% of patients in whom PSVT occurs spontaneously.¹¹

Both the presence of neurologic symptoms without arrhythmias and the unusual features of the PSVT led us to consider alternate explanations in these patients referred for cardiac evaluation. A primary neurologic abnormality causing seizures and subsequent initiation of arrhythmias was an hypothesis that would explain all findings. Epileptiform discharges on the EEG of both patients supported this disorder hypothesis.

A correlation between the EEG abnormalities and the cardiac arrhythmias would provide important evidence implicating the epileptic



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Fig 2 Paroxysmal supraventricular tachycardia. Patient No 2. This tachycardia had been present for over 12 hours when its termination was recorded on this monitor lead. The last QRS was the result of a sinus beat.

described at the time of the second attack. Phenobarbital 30 mg orally twice daily was added to digoxin and propranolol 10 mg orally twice a day was begun in 1975. He continued to have dizzy spells, bradycardia and tachycardia. He lost consciousness again in December 1975, was taken to a hospital emergency room and was found to have a rapid supraventricular tachycardia. Phenobarbital was increased to 30 mg three times daily and propranolol was increased to 20 mg also three times a day. Quinidine 200 mg four times daily was begun in February 1976 and digoxin and phenobarbital were continued. In September 1976 he again lost consciousness. His heart rate recorded by the school nurse was 180 beats/minute. He was admitted to a hospital and PSVT converting to sinus rhythm was recorded on a monitor lead (Fig 3). He was referred for further evaluation and treatment.

The vital signs were normal and the cardiovascular and neurologic systems were normal by clinical examination. An electrocardiogram recorded at the time of admission was normal.

During the course of hospitalization the patient was observed with continuous ECG monitoring in the Coronary Care Unit. A variety of arrhythmias were documented including sinus tachycardia (rate 210 beats/minute), sinus arrest (2.6 second pauses), junctional rhythm with retrograde block, junctional rhythm with retrograde conduction, multifocal ventricular tachycardia, first-degree atrioventricular (A-V) block, Mobitz Type I second-degree A-V block and high grade A-V block. During periods of sinus rhythm there were frequent episodes of sinus arrest followed by appearance of an ectopic atrial pacemaker at a rate slower than the sinus rate (similar to the rhythm recorded in Patient No 1). No symptoms occurred during arrhythmias.

Results of electrophysiologic testing. Basic conduction intervals (Table 1) and sinus node recovery times were normal. Using stimulation sites in the right atrium and right ventricle electrophysiologic tests were performed. The A-V conduction system was tested with fixed rate pacing and the extrastimulus technique. The A-V conduction system was normal and no tachycardia was initiated.

Electroencephalogram findings. The background rhythm of the EEG consisted of a well developed alpha rhythm at a frequency of 9 Hz. The principal abnormalities consisted of (1) irregular intermittent theta and delta transients in the temporal regions throughout the waking record and (2)

bilaterally synchronous 3 to 4 per second spike and wave discharges maximal in amplitude in the frontal and central regions (Fig 4). Despite the focal theta and delta transients in the left temporal region, no focal (as opposed to bilaterally synchronous) cortical spiking was detected. The focal slowing suggested the presence of a structural lesion in the left temporal region. The synchronous spike wave discharges would be consistent with a diagnosis of cortical reticular epilepsy in a symptomatic patient. Supraventricular tachycardia was detected by simultaneous monitoring of the electrocardiogram during the EEG. However, the supraventricular tachycardia did not reflect a consistent temporal relation to occurrence of EEG abnormalities.

Clinical course. A ventricular demand pacemaker was implanted in October 1976. He began taking phenytoin 100 mg three times a day. He continued to have supraventricular tachycardia. Treatment with digoxin 0.25 mg three times daily was begun. Supraventricular arrhythmias persisted and digoxin was discontinued and propranolol and a combination of propranolol and disopyramide were tried. No combination of drugs prevented tachycardia but the patient did not have another episode of loss of consciousness. The patient was found dead in a swimming pool in April, 1977. At the time of death, the pacemaker was functioning normally. The brain was normal at autopsy.

Discussion

The ages of these patients and several other factors strongly suggest that the arrhythmias in these two patients did not cause the neurologic symptoms. Paroxysmal supraventricular tachycardia is not usually associated with syncope in children and one patient had episodes of dizziness and disorientation which were not accompanied by palpitations. Also during episodes of loss of consciousness accompanied by tachycardia the tachycardia persisted after consciousness returned. Neurologic symptoms secondary to an arrhythmia usually last as long as the arrhythmia does or until the victim has fallen to a recumbent position. When consciousness returned our patients were able to resume normal activities (in

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IMPORTANT
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discharges as a cause for the cardiac arrhythmias. Despite the occurrence of the cardiac arrhythmia during EEG monitoring in Patient No 2 such a correlation was not established. This finding is not surprising in light of two facts. First, even when abnormally excitable neural tissue lies in immediate proximity to the scalp (e.g. *epilepsia partialis continua*, arising from precentral gyrus) a close correlation between epileptiform discharges on EEG and the clinical seizure can be established in less than 50% of cases. Second, accurate sampling of epileptiform activity in depths of the brain by sampling scalp EEG is exceedingly difficult. Since the brain regions implicated by stimulation studies as causing arrhythmias are remote from the scalp (e.g. diencephalon and orbital frontal cortex), difficulties in establishing a close correlation would be expected. Thus the failure to establish a one to one relationship between the PSVT and the scalp EEG abnormalities in no way excludes seizures as a cause of the arrhythmias.

Walsh and colleagues¹ described a patient in whom a supraventricular arrhythmia occurred immediately following the onset of epileptiform discharges on the EEG. Unfortunately, electrophysiologic testing of that patient was not done and the absence of an intrinsic cardiac abnormality can not be assumed.

Abolition of both the arrhythmia and the neurologic symptoms in Patient No 1 by a single antiepileptic agent, carbamazepine, is consistent with the primary neurologic cause of a cardiac arrhythmia postulated. Carbamazepine has some antiarrhythmic effects on ventricular tachycardia induced by digitalis or coronary artery ligation in dogs.⁴ It is however also related to the tricyclic antidepressants that have arrhythmogenic potential in man. The effect of carbamazepine on arrhythmias in humans is not known.

The findings in our two patients in which arrhythmias appeared to be secondary to partial seizures strengthen the argument that some arrhythmias have a neural origin. Arrhythmias have been induced by stimulation of the diencephalon of experimental animals and bradycardia⁵ and tachycardia⁶ have been reported in humans with epilepsy. Recent investigation of the neural influence on arrhythmias has identified an important role for psychologic stress. Potentially lethal arrhythmias have been linked to

psychologic stress in two patients who had no known cardiac abnormalities.⁷⁻⁹ Future study of the origin of arrhythmias may include studies of the neurologic system.

Summary

This report describes a clinical syndrome of arrhythmias that may have neural origin. Two patients presented with episodes of loss of consciousness, disorientation and paroxysmal supraventricular tachycardia (PSVT). One patient reported experiencing neurologic symptoms with out tachycardia. When electrophysiologic testing with intracardiac recordings and programmed stimulation yielded no abnormalities that could account for the arrhythmias, a primary neurologic abnormality was sought. The electroencephalograms of both patients showed epileptiform discharges that supported this hypothesis. Arrhythmias and neurologic symptoms were controlled by treatment with the antiepileptic drug carbamazepine in one patient. Findings in these two patients suggest that in some patients arrhythmias may be a manifestation of seizures.

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Table 1 Microbiology of infective endocarditis

| | Patients | | | |
|-----------------------------------|-------------------------|-----|-------------------------|-----|
| | 1951 through 1967 | | 1972 through 1976 | |
| | No | % | No | % |
| <i>Viridans streptococci</i> | 91 | 53 | 81 | 37 |
| Group D streptococci | 28 | 16 | 35 | 17 |
| <i>Staphylococcus aureus</i> | 24 | 14 | 33 | 15 |
| <i>Staphylococcus epidermidis</i> | 4 | 2 | 13 | 6 |
| Gram negative bacilli | 10 | 6 | 24 | 11 |
| Other microorganism | 1 | 1 | 25 | 11 |
| Negative blood cultures | 14 | 8 | 7 | 3 |
| Total | 172 | 100 | 219 | 100 |

Including fungi. (From Wilson W R and Washington J A II Infective endocarditis—a changing spectrum? (Editorial) Mayo Clin Proc. 52:24 1977. Reproduced by permission.)

1970s however the average number of cases of IE increased from 24.5 per year 20 years ago to 44 per year during the 1970s, and the number of patients with viridans streptococcal infections increased from 11.1 to 16 per year. It is clear that there are not only patients with viridans streptococcal IE, but also more patients with IE caused by other microorganisms. Part of this changing spectrum is the result of nosocomially acquired infections associated with the increased use of intracardiac prostheses, life support mechanisms, monitoring systems and invasive diagnostic techniques. Another factor in the changing microbiologic spectrum of IE is the apparent increase in the number of patients with IE associated with intravenous drug abuse. Nosocomially acquired IE or IE associated with intravenous drug abuse is often due to gram negative bacilli, *Candida* and opportunistic microorganisms—uncommon causes of IE in the 1950s.

Despite the changing spectrum of IE, at least 75% of infections are caused by streptococci or staphylococci. The selection of antimicrobial agents for the therapy of infections caused by these microorganisms depends on the penicillin susceptibility of these isolates. An understanding of the differences between streptococci and staphylococci that are susceptible to penicillin and those that are resistant to penicillin is essential for the selection of appropriate antimicrobial agents and frequently for determining the length of antimicrobial therapy.

Role of blood cultures in diagnosis of IE

In patients with suspected IE the most important laboratory finding is the isolation of bacteria or fungi from at least two or more blood cultures obtained at intervals during a 48-hour period. Bacteremias associated with IE are usually continuous^{6,7} and if any blood cultures are positive, most of the other cultures drawn will also be positive.^{8,9} Although bacteremia is probably continuous, Weiss and Ottenberg¹⁰ found 22 showers of larger numbers of bacteria temporally related to an increase in patients' body temperatures. Wright¹¹ was unable to document a temporal association with fever. The order and magnitude of bacteremia is usually relatively constant. In 83% of cases the quantitative blood culture contained less than 100 colonies per milliliter.^{12,13} Studies have shown that cultures of peripheral venous blood are as likely to be positive as those of arterial blood.^{14,15} Blood cultures should not be obtained through a preexisting intravenous catheter because pericatheter contaminants or colonizers may be drawn up into the blood sample and contaminate the blood culture medium.¹⁶

Bell and Waisbren¹⁷ reported that 3% of cases of IE were diagnosed with the first blood culture and in only six cases were more than two blood cultures necessary. Werner and associates, in a similar study, found that streptococci were isolated in 96% of cases from the first blood culture and in 98% from one of the first two blood cultures. Staphylococci were isolated from the first culture in 90% and from one of the first two cultures in 100% of cases. Antimicrobial therapy given within 2 weeks before blood cultures were obtained reduced the positive cultures in 7% of cases of streptococcal endocarditis from 94% to 87% ($P < 0.02$).¹⁸ In cases of IE caused by microorganisms other than streptococci and staphylococci, the causative agent was isolated from 87% of cases in the first blood culture and from 100% in one of the first two blood cultures.¹⁹

In conclusion, on the basis of the above data, patients who have not received prior antimicrobial therapy, it is rarely necessary to obtain more than three separate sets of blood cultures over a 24-hour period on two consecutive days in patients suspected of having IE. The time of collection of blood cultures just before an expected increase in temperature may potentially increase the likelihood of a positive blood culture.

Reviews

Infective endocarditis therapeutic considerations

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During the preantibiotic era recovery from serious bacterial infections was not uncommon. That patients survived these infections is testimony to the major role played by host defense mechanisms in controlling or eradicating many types of bacterial infections. This is not the case with infective endocarditis (IE). Host defense mechanisms play little role in the control of IE and before the discovery of antibiotics the mortality rate of patients with IE was virtually 100%. In no other infection does cure seem to be so dependent upon the administration of appropriate bactericidal antimicrobials. The pathologic events that result in the formation of valvular vegetations composed of dense networks of avascular fibrin platelet matrices appear to protect microorganisms buried within from phagocytes and other host defense mechanisms.

Effective antimicrobial therapy exists for most patients with IE. The role of the microbiology laboratory in the selection of appropriate antimicrobial therapy is probably more important in the management of patients with IE than in that of any other infectious disease process. The purpose of this paper is to discuss the microbiologic spectrum of IE, the role of the microbiology laboratory and the rationale for the selection of antimicrobial therapeutic regimens and to consider general principles for the medical and surgical management of patients with IE.

Microbiologic cause of IE

Virtually any microorganism is capable of causing IE. Table I lists the microbiologic causes of IE in 172 patients seen at the Mayo Clinic from 1951 through 1957 and compares these data with those from 219 patients with IE treated at the Mayo Clinic 20 years later. The data presented in Table I suggest that the microbiologic causes of IE in the 1950s differed from those of the 1970s. The increasing number of reports describing uncommon causes of IE is probably attributable to two factors: (1) improved microbiologic techniques and (2) a changing microbiologic spectrum. The impact of improved microbiologic techniques is apparent in patients with gram negative bacillary other infections and culture negative endocarditis. Some gram negative bacilli such as *Haemophilus* species are slow growing microorganisms with special growth requirements. These fastidious microorganisms constitute a major portion of the gram negative bacillary cases of IE in the latter group of patients seen at the Mayo Clinic. Of the 25 patients seen with IE in the 1970s caused by other microorganisms six had infections with anaerobic gram positive cocci. In the 1950s anaerobic microbiology was largely a research tool and patients with IE due to anaerobic bacteria would have been classified as culture negative. Although improved techniques may explain some of the differences between IE of the 1950s and that of the 1970s, the experience at the Mayo Clinic and elsewhere indicates that the bacterial spectrum of IE is changing. The percentage of patients with viridans streptococcal IE seen at the Mayo Clinic declined from 53% in the 1950s to 37%.

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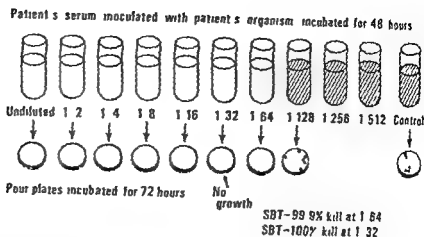


Fig 2 In vitro susceptibility testing serum bacterial test

can) the serum sample should be obtained at the anticipated peak concentration of the agent administered intermittently. A standard inoculum of the patient's bacteria is transferred to each tube and the tubes are incubated at 37° C for 48 hours. Tubes showing no visible evidence of growth and the last tube showing growth are subcultured into pour plates as described above. The results are expressed as the highest dilution of patient serum which kills 99.9 to 100% of the inoculum. Although it is difficult to interpret accurately the results of the SBT, considerable clinical experience suggests that antibiotic treatment should be adjusted to achieve a peak serum concentration of antimicrobials which results in an SBT of 1/8 or more.

It is desirable to measure serum concentrations of antibiotics from the same specimen of serum used to determine SBT. The serum concentrations assist in the interpretation of the SBT. A low SBT may be related to a simultaneously low serum concentration of antimicrobial rather than to a lack of bactericidal effect and this suggests that the dosage should be increased. Serum concentrations should also be measured periodically throughout the course of treatment to ensure adequate therapeutic levels in excess of the MBC and to avoid accumulation in the serum of potentially toxic concentrations of antimicrobials.

Occasionally, with unusual organisms or those resistant to multiple drugs or as a guide for determining optimal combinations of antimicrobials in vitro tests of synergism between antimicrobials may be desirable. Methods for determining antimicrobial synergy have been described.¹³⁻¹⁵

Treatment of IE—general considerations

A number of general principles should be adhered to in the treatment of all patient IE.

1 It is important to establish the microbial diagnosis if possible before starting antibiotic therapy. In the subacute form of IE, patients often have been ill for weeks or months, and there is usually no great urgency to initiate antibiotic therapy. Failure to establish the microbial cause in cases of suspected IE may require prolonged hospitalization with increased cost to the patient. Multiple iatrogenic complications related to the use of inappropriate therapy, possible relapse of the infection. In contrast, patients with acute septic IE, the use of antibiotics should not be delayed until the blood cultures or other laboratory studies are known. Therapy should be begun promptly once blood has been obtained for the initial set of cultures. The importance of the use of bacterial antimicrobials and SBT determinations is emphasized above.

2 In urgent cases in which empiric antibiotic therapy must be initiated before the causative agent has been identified, the regimen should include a combination of antibiotics effective against enterococci and penicillinase-producing staphylococci.

3 It is preferable to treat patients in facilities where emergency cardiac valve replacement may be performed if necessary. Patients with aortic valve IE may experience acute aortic insufficiency with severe congestive heart failure. Immediate cardiac valve replacement in such patients may offer the only hope of survival.

4 In general antimicrobial therapy should be

Broth containing patient's organism and serial dilutions of antibiotic incubated 18 hr

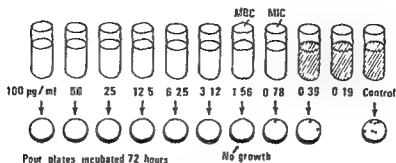


Fig 1 In vitro susceptibility test, minimum bacterial concentration

out the limitations of this recommendation are obvious. An important exception to the reports that state that blood cultures are usually positive in patients with IE is that of patients with fungal IE. Patients with IE caused by *Candida* species often have positive blood cultures; however, other causes of fungal IE, notably *Aspergillus* species, are usually associated with negative blood cultures. Diagnosis may occasionally be established by staining and culturing emboli removed surgically from peripheral vessels.¹ More often, the diagnosis of fungal IE is made at the time of cardiac valve replacement or at autopsy.

In vitro susceptibility testing

It is important to determine accurately the in vitro susceptibility of organisms causing IE. The most widely used test and the simplest to perform is the minimum inhibitory concentration (MIC)—the lowest concentration of antibiotic which will inhibit the growth of the causative bacteria. MIC may be measured by disk diffusion, agar dilution, or broth dilution methods.

The minimum bactericidal concentration (MBC)—the lowest concentration of antimicrobial which will kill 99.9 to 100% of the inoculum—is also helpful in determining optimal therapy. The broth dilution technique is used to determine MIC (Fig 1). Briefly described, 10 serial twofold dilutions of the desired antibiotic are prepared in nutrient broth in sterile test tubes. The concentration of antibiotic in the 10 tubes of nutrient broth decreases sequentially: 100 µg/ml in tube 1, 50 µg/ml in tube 2, 25 µg/ml in tube 3, and so on to 0.19 µg/ml in tube 10. A standard inoculum of the patient's bacteria is then added to each tube. After overnight

incubation at 37°C, the tubes are examined. The lowest concentration of antibiotic which completely inhibits visible growth as indicated by lack of turbidity in the media is the MIC. From each of the tubes that have no visible turbidity and from the first tube exhibiting the turbidity, aliquots are removed and subcultured into media for pour plates. After 48 and 72 hours of incubation, the lowest concentration of antibiotic which kills 99.9% of the inoculum (less than 10 colonies per plate) or 100% of the inoculum is recorded as the MBC.

The disk diffusion or agar-dilution MIC provides valuable information for the initiation of antimicrobial therapy. However, most clinicians experienced in the treatment of patients with IE believe that broth-dilution MIC and MBC are more accurate in indicating susceptibility. The concentration of antimicrobial agents achieved in fibrin clot vegetations may be less than that measured in serum, and dosages of antimicrobials should be adjusted so that ideally the peak serum concentration of antimicrobial exceeds the MBC.

The serum bactericidal test (SBT) is a modification of the broth dilution test of antimicrobial susceptibility. Instead of serial dilutions of an antimicrobial solution, serial twofold dilutions are prepared of the patient's serum containing the antibiotic that has previously been administered to the patient (Fig 2). Serum samples should be obtained at the anticipated peak serum antimicrobial concentration, usually 1 hour after administration of an antibiotic. If the patient is receiving two antimicrobials, one continuously and one intermittently (that is, continuous intravenous penicillin and intramuscular streptomycin),

tive therapy outlined below or presented in standard texts and references

Penicillin sensitive viridans and nonenterococcal group D streptococcal IE (MIC $\leq 0.1 \mu\text{g/ml}$)

Penicillin sensitive viridans and nonenterococcal group D streptococci are the most frequent causes of IE, constituting at least 45% of all cases.¹⁻⁴ These organisms are part of the normal microbial flora of the oral cavity and gastrointestinal tract. Species of viridans streptococci are especially common in the oral cavity where they form plaques on the surface of teeth. At least one species *Streptococcus mutans* is important in the production of dental caries.²⁷ It has been recognized for many years that dental manipulations may result in transient polymicrobial bacteremia, and a history of recent dental procedures often antedates the onset of symptoms of IE.²⁸⁻³¹ Viridans streptococci are considered noninvasive saprophytes and why these rather placid organisms and not other more aggressive microbes found in the oral cavity, result in IE has been a subject of considerable interest. Recent studies have demonstrated that viridans streptococci *S. bovis* and some enterococci are considerably more adherent to the endothelium of heart valves than are other bacteria. This increased adherence is probably due to the production of dextran which increases bacterial stickiness.³²⁻³⁵ Not coincidentally then viridans and nonenterococcal streptococcal IE is most often caused by dextran producing strains—*S. sanguis*, *S. mutans*, *S. bovis*—and IE caused by non dextran producing strains—*S. salivarius*—is rare.³⁶

Hunter originally suggested the use of combined penicillin streptomycin therapy for treatment of viridans streptococcal IE based on in vitro studies demonstrating synergy against isolates of viridans streptococci.³⁷ That the combination of penicillin and streptomycin is superior to penicillin alone in the treatment of these infections is supported by data collected from studies of experimental animal IE. Combined penicillin and streptomycin was more effective than penicillin alone in preventing experimental endocarditis,³⁸ and in the treatment of established infection. In patients with IE caused by viridans streptococci who were treated with dihydrostreptomycin and low dose penicillin therapy,³⁹ early studies reported relapse rates of 6 to 11%.

Table II lists three generally accepted methods and alternatives for the antimicrobial therapy of penicillin sensitive viridans and nonenterococcal group D streptococcal IE. Recently,⁴⁰ reported⁴¹ a prospective study of 68 patients with streptococcal IE (54 patients with *S. viridans* and 14 with *S. bovis* infections) who were treated with short term combined intramuscular therapy with procaine penicillin and streptomycin. In none of these patients did the infection recur and the mortality rate was 3%. Earlier, a series (J. E. G.) reported only one relapse among surviving patients treated for 2 weeks with varying dosages of intramuscular penicillin and streptomycin.⁴²⁻⁴⁴ Together with our 68 patients, the additional 66 patients constitute a total of 134 patients who were treated similarly, with no one relapse (0.7%). Some authors suggest that patients whose symptoms have been present for more than 3 months may be at higher risk of relapse and that treatment should be continued with penicillin G alone for an additional 3 weeks. However, 14 of our 68 patients (21%) who were treated with short term therapy had symptoms for more than 3 months and in none was there a relapse. Moreover, two of our 68 patients had a relapse elsewhere after 4 weeks of intravenous penicillin G therapy alone and both patients were cured with short term combined therapy.

Some viridans streptococci are relatively resistant to penicillin (MIC $> 0.1 \mu\text{g/ml}$, MBC $\geq 3.12 \mu\text{g/ml}$). Some investigators⁴⁵⁻⁴⁷ feel that patients with infections caused by these relatively penicillin resistant microorganisms should receive antimicrobial therapy identical to that for enterococcal endocarditis (see below and Table III). In our study, 37% of isolates were relatively penicillin resistant according to our criteria.⁴⁸ All of these patients were cured of infection with 2 weeks of intramuscular combined penicillin streptomycin therapy.

Wolfe and Johnson⁴⁹ found no relapses in a retrospective study of 30 patients with IE caused by penicillin sensitive viridans streptococci who were treated with a mean daily dose of 1 million units of penicillin for 30.4 days and 1 million units of streptomycin for 13.4 days. In unpublished data these authors cite in excess of 60 additional patients treated similarly without relapse. T. J. Pett and Hurst⁵⁰ reported no relapses in 60 patients in whom a similar therapeutic regimen had been used.

Streptomycin associated vestibular toxicity

administered parenterally rather than orally. Absorption from the gastrointestinal tract of orally administered antimicrobial agents may be unpredictable.

5 Patients who are receiving treatment for IE should be examined daily throughout their hospital course. Subtle changes in body weight, blood pressure, cardiac auscultatory findings, jugular venous distention, and so on, may presage abrupt hemodynamic decompensation. Clinicians should also be alert for the occurrence of large arterial emboli, especially in patients with IE caused by *Haemophilus* species or by fungi.

6 Within 48 hours after initiation of specific antimicrobial therapy, blood cultures should be used to assess the efficacy of treatment. Persistently positive blood cultures in spite of apparently appropriate treatment could indicate myocardial, aortic root, or distant abscesses, tolerance of bacteria to antimicrobial agents, or error in administration or dosage of antimicrobial agents.

7 After antimicrobial therapy has been initiated, careful attention should be directed to eliminating the possible portal of entry of the causative agent—for example, poor dental hygiene or urinary tract infections with or without stones. Dentulous patients with IE who are not medically ill should have dental x-ray films and an oral surgery consultation so that necessary dental work can be performed while the patient is receiving treatment for IE. Because of the association with inflammatory bowel disease and carcinoma of the colon, patients with IE caused by *Streptococcus bovis* should have a proctoscopy and colon x-ray studies while receiving antimicrobial therapy.

8 If severe heart failure that is unresponsive to medical therapy ensues before completion of antimicrobial therapy, prompt cardiac valve replacement should be considered. Procrastination in an attempt to complete a course of antimicrobial therapy preoperatively will only increase the surgical mortality. The hemodynamic status of the patient should be the most important factor in determining the timing of cardiac valve replacement.

9 Before dismissal from the hospital, patients and their families should receive adequate instructions in prophylactic measures for IE. IE often has multiple and complex medical, surgical, and laboratory facets, and patient education

Table II Treatment of penicillin sensitive viridans or nonenterococcal group D streptococcal infective endocarditis (MIC $\leq 0.1 \mu\text{g/ml}$)

| Treatment of patients not allergic to penicillin | Alternative treatment of patients allergic to penicillin |
|---|--|
| Procaine penicillin 1.2 million units IM q6h plus streptomycin 7.5 mg/kg IM q12h for 14 days | Cephalothin 1 g IV q4h for 28 days or Vancomycin 15 mg/kg IV q6h for 28 days |
| Aqueous penicillin 20 million units IV per day for 28 days plus streptomycin 7.5 mg/kg IM q12h for the first 14 days of treatment | |
| Aqueous penicillin 20 million units IV per day for 28 days | |

Modification of method of Wolfe and Johnson¹¹

concerning prophylaxis is an important although frequently overlooked component.

10 Follow-up blood cultures should be obtained at 1 and 2 months after completion of antimicrobial therapy. Relapses, if they occur, most often appear within the first 2 months after completion of treatment. Infections caused by fungi, *Staphylococcus epidermidis*, and fastidious microorganisms such as *Haemophilus* species may relapse later than 2 months.

11 Finally, physicians should respect the seriousness of IE and should resist the temptation to compromise in the duration and means of administration of therapy or to switch to less effective antimicrobial agents. After initiation of therapy, some patients with IE, especially those with penicillin-sensitive streptococcal infections, will experience a dramatic improvement in general well-being and disappearance of fever. These improvements should not be interpreted as an indication that the antimicrobial may be switched to orally administered agents or that the length of treatment may be shortened. Symptomatic control of most hypersensitivity reactions should be attempted before a change is made to alternative therapy. If major hypersensitivity reactions or other complications occur which cannot be controlled by symptomatic measures, alternative therapy may be used. Clinicians should use only those accepted forms of alterna-

Table IV Treatment of penicillin sensitive staphylococcal infective endocarditis (MIC $\leq 0.1 \mu\text{g/ml}$)

| Treatment of patients not allergic to penicillin | Alternative treatment of patients allergic to penicillin |
|--|---|
| Aqueous penicillin G 20 million units per day for 4 to 6 weeks | Cephalothin 1 g. IV q4h or cefazolin 1 g. IV or IM q6h for 4 to 6 weeks or Vancomycin 7.5 mg./kg. IV q6h for 4 to 6 weeks |

from nonenterococci (*S. bolus*) by their growth in broth containing 6.5% sodium chloride.

A very important characteristic of enterococci is that they are inhibited but not killed by penicillin alone. A combination of penicillin (or ampicillin, carbenicillin or ticarcillin) and aminoglycosides (streptomycin, kanamycin, gentamicin, tobramycin or amikacin) acts synergistically against enterococci, and combined treatment is necessary for the successful therapy of enterococcal IE.^{4, 5}

Table III outlines standard antimicrobial therapy for enterococcal IE. Moellering and associates and others have shown that only about 60% of enterococci show synergy of bactericidal effect when incubated with penicillin plus streptomycin compared with penicillin alone.^{4, 6, 7} The approximate 40% of strains which are highly resistant to streptomycin (MIC $> 2,000 \mu\text{g/ml}$) do not show this synergistic effect. The combined use of penicillin and gentamicin has been shown to result in synergistic bactericidal effect in vitro against most enterococci, including strains that are highly resistant to streptomycin. Additionally, combinations of penicillin and tobramycin, ampicillin and gentamicin and vancomycin and gentamicin were found to act synergistically in vitro against highly streptomycin resistant strains of enterococci. Hook and associates and Carrizosa and have demonstrated in the experimental rabbit model of IE that the combination of penicillin and gentamicin was superior to the combination of penicillin and streptomycin in the treatment of infection caused by highly streptomycin resistant enterococci.

The significance of streptomycin resistance in human IE is not clear. At present, insufficient

data exist to indicate conclusively the superiority of the penicillin-gentamicin combination over the penicillin-streptomycin combination for the treatment of streptomycin-resistant enterococcal IE. In patients with infections caused by streptomycin-resistant microorganisms, one possible course might be to initiate therapy with penicillin plus streptomycin and then measure the SBT. If the SBT is low (< 1.8), the dosage of penicillin could be increased from 20 million units per day to 40 million units per day and the SBT could be remeasured. If the SBT is still less than 1, gentamicin could be substituted for streptomycin and the SBT could be rechecked again. A decision could then be made concerning the relative therapeutic advantage of streptomycin or gentamicin.

Some patients with enterococcal IE require simultaneous antistaphylococcal therapy for unrelated infections. In other cases, patients with acute IE such as that in benzodiazepine addicts may require initial antimicrobial therapy for IE caused by either staphylococci or enterococci. In vitro studies have demonstrated synergy with nafcillin or oxacillin plus gentamicin against some strains of enterococci.^{8, 9} However, Leach and associates¹⁰ in the experimental rabbit model demonstrated that combination of rifampin-resistant penicillin and gentamicin was not as effective as penicillin plus streptomycin or gentamicin in the treatment of experimental enterococcal IE. Until more data are available, nafcillin, oxacillin or methicillin should not be substituted for penicillin G in the treatment of enterococcal IE. Likewise, cephalosporins should not be combined with streptomycin or gentamicin as a substitute for penicillin in the treatment of enterococcal IE.^{11, 12} In these patients, therapy with three antimicrobial agents (that is, penicillin, streptomycin and nafcillin) would be preferable.

Because experience with the use of all penicillins to penicillin in patients with enterococcal IE is limited, efforts should be made to continue the use of penicillin in patients who have an adequate history of previous "reaction" to penicillin. In patients who experience minor hypersensitivity reactions during the course of treatment with penicillin, in these patients symptoms can usually be controlled with antihistamines and corticosteroids. If penicillin therapy has to be interrupted, then

was 3% among our 68 patients who were treated with short term intramuscular therapy.²¹ This is similar to that reported by Tompsett and

²² and by Wolfe and Johnson.⁴ Streptomycin associated toxicity is more likely to occur in the elderly and in patients who have abnormal renal function. Streptomycin should be used with caution if at all in these patients. Short term intramuscular combined therapy should not be used in thrombocytopenic patients or in patients who have severe heart failure, shock or other conditions in which there is presumed poor peripheral perfusion and possible decreased absorption of antimicrobial agents from sites of intramuscular injection.

Penicillin sensitive streptococcal IE may also be treated successfully with high dose intravenous penicillin G alone. The treatment should not be less than 4 weeks in duration. In earlier clinical trials more than 50% of patients receiving 0.5 to 1 million units of penicillin per day for less than 2 weeks were treatment failures.⁴ When the dosage of penicillin was increased to 14 to 16 million units per day for 10 to 14 days relapse rates of 15% were still encountered. In two recent retrospective studies no relapses occurred in patients treated for 4 weeks or more with high dose parenteral penicillin alone.⁵

Based on data currently available it appears that the three regimens outlined above and in Table II are roughly equivalent in their cure rate. The advantages of treatment for 2 weeks with intramuscular antimicrobials over treatment for 4 weeks with intravenous antimicrobials or combined intramuscular and intravenous therapy or 4 weeks however are clear—namely, shortened hospitalization period with reduced cost to patients, more efficient use of hospital personnel and facilities and avoidance of potentially hazardous complications associated with the use of intravenous therapy. A disadvantage of combined therapy is the small risk of streptomycin associated vestibular toxicity. This toxicity may be minimized by restricting the use of streptomycin in patients 65 years old or older or in patients with abnormal renal function and by following patients closely for signs of developing vestibular dysfunction. Elderly patients and patients who have abnormal renal function should be treated with penicillin G alone. Another disadvantage to the use of short term combined intramuscular therapy is the frequent intramuscular injections that are necessary. In

Table III Treatment of penicillin resistant (enterococcal) infective endocarditis (MIC $\geq 0.1 \mu\text{g/ml}$)

| Treatment of patients not allergic to penicillin | Alternative treatment of patients allergic to penicillin |
|--|--|
| Penicillin 20 to 40 million units IV per day or ampicillin 12 g IV per day | Vancomycin 7.5 mg/kg IV q6h |
| plus | plus |
| Streptomycin > 7 mg/kg IM q12h or gentamicin 1 mg/kg IM or IV q8h for 4 to 6 weeks | Streptomycin 7.5 mg/kg IM q12h or gentamicin 1 mg/kg IM or IV q8h for 4 to 6 weeks |
| | or |
| | Desensitize to penicillin |

our experience however the intramuscular injections were generally well tolerated. The tolerance was enhanced somewhat when the patient understood that with this form of therapy mobility in the hospital is increased and the period of hospitalization is decreased.

In patients who are unable to take penicillin because of hypersensitivity cephalosporins should be used with caution because of the possibility of cross sensitivity reaction. Cephalothin and vancomycin have been used successfully in the treatment of viridans and nonenterococcal group D streptococcal infections.^{4,5} Desensitization of patients to penicillin should be attempted only when alternative forms of therapy are impractical or unavailable.

Until more data are available treatment of IE caused by other penicillin sensitive streptococci such as group A beta hemolytic streptococci, group B streptococci, *Streptococcus pneumoniae* and the like should be with high-dose penicillin (20 million units per day) intravenously for 1 month. Patients who are unable to take penicillin may be treated for 1 month with cephalothin or vancomycin in dosages outlined in Table II.

Penicillin resistant streptococcal IE—enterococci (MIC $\geq 0.1 \mu\text{g/ml}$)

The group D streptococci enterococcus group contains the organisms *S. fecalis* and its two variants (zymogenes and liquefaciens), *S. faecium* and *S. durans*. Almost all of the enterococci that cause IE are *S. fecalis* and most of these are of the variety liquefaciens. Group D streptococci may be distinguished from viridans streptococci by their ability to grow in media containing bile and the enterococci may be further distinguished

authors have expressed doubts about the usefulness of cefazolin in the treatment of human IE due to *S. aureus*.¹⁴ However, most clinicians believe that methicillin, oxacillin, nafcillin, cephalothin and cefazolin are roughly equivalent in their efficacy in the treatment of patients with IE due to *S. aureus*. Vancomycin may be used in patients who are unable to tolerate penicillin or cephalosporins.

Table V outlines accepted antimicrobial therapy in patients with penicillin resistant staphylococcal IE. Sabath and associates¹⁵ recently describes staphylococci that are inhibited by low concentrations but are not killed by high concentrations of penicillinase resistant penicillins. This disparity between MIC and MBC known as tolerance is of uncertain clinical significance. More clinical experience is needed before conclusions can be made regarding the need for different therapeutic approaches to these patients with tolerant *S. aureus* infections.

The treatment of patients with endocarditis caused by penicillinase resistant *S. aureus* is somewhat controversial. That the antimicrobial therapeutic regimen should include a penicillinase resistant penicillin (nafcillin, oxacillin or methicillin) a cephalosporin or vancomycin is unquestioned. Controversy surrounds the desirability of the addition of other antimicrobial agents that are synergistic against *S. aureus* when combined with the standard antistaphylococcal agents compared with the activity of penicillins or cephalosporins alone. Sande and Johnson¹⁶ demonstrated that the combination of penicillin and gentamicin acted synergistically in vitro against a strain of penicillin susceptible *S. aureus*. The combination of nafcillin and gentamicin showed synergy in vitro against penicillinase producing *S. aureus* compared with the activity of nafcillin alone.¹⁷ In IE due to *S. aureus* in experimental animals the organisms were eradicated more rapidly from cardiac vegetations when animals were treated with the combination of gentamicin and nafcillin than with nafcillin alone.¹⁸ Insufficient data exist to suggest that the combination of gentamicin and nafcillin should be used as standard therapy of human IE caused by *S. aureus*. The potential increased toxicity of the use of combined treatment should be considered and weighed against the theoretic benefit. Gentamicin alone should not be used as therapy for IE due to *S. aureus*.

Mutant variants of *S. aureus* emerge in experimental animals with IE caused by *S. aureus*. These animals are treated with gentamicin and the use of gentamicin fails to sterilize cardiac vegetation.¹⁹

A retrospective study of the use of single and combination treatment with gentamicin in patients with IE due to *S. aureus* showed benefit from the use of the combination over single drug treatment.²⁰ A cooperative prospective study is currently under way comparing combination of nafcillin gentamicin therapy with the use of nafcillin alone in patients with penicillinase producing IE caused by *S. aureus*.

IE caused by methicillin resistant *S. aureus* is rare and treatment with vancomycin may be necessary.¹ Rifampin in combination with other antimicrobial agents may also prove useful in the treatment of methicillin resistant *S. aureus*.²¹

S. epidermidis is one of the most common agents causing infection in patients with prosthetic heart valves and cerebrospinal fluid shunts.²² Whereas methicillin resistant strains of *S. aureus* are rare, *S. epidermidis* resistant to methicillin occurs commonly. The frequency of methicillin resistant *S. epidermidis* isolates has been reported to range from 10 to 63%.²³ Archer²⁴ reported that 63% of 27 isolates from patients with prosthetic valve endocarditis or cerebrospinal fluid shunts were resistant to methicillin. Archer made an extensive study of in vitro susceptibility and resistance patterns of these 27 isolates. Against methicillin most isolates showed excellent activity against most isolates. Among aminoglycosides tested, gentamicin was the most active and no resistant cell populations were identified among susceptible isolates. Rifampin was the single most active agent against isolates but high level resistance to rifampin emerged in some isolates after 8 to 24 hours of incubation. Because of the high frequency of methicillin resistance the initial regimen for treatment of IE caused by *S. epidermidis* should include agents that are active against methicillin resistant microorganisms. On the basis of currently available cephalothin, cefazolin, cefazolin alone or in combination with gentamicin and vancomycin, gentamicin and vancomycin appears to be the preferred choice for treatment of IE caused by *S. epidermidis*.

patients subsequent resumption of therapy with penicillin is more likely to provoke serious reaction and alternative therapy should then be instituted. In these patients or in patients with a history of anaphylaxis or other major hypersensitivity reaction to penicillin, combinations of ampicillin, streptomycin, or vancomycin and gentamicin may be used.^{4, 6, 77}

Combined penicillin aminoglycoside therapy is effective treatment for enterococcal IE. No relapses occurred among 36 patients reported by Mandell and associates⁷⁸ and one relapse occurred among 30 patients reported by Geraci and colleagues.⁷⁹ However, adverse reactions associated with the use of aminoglycosides are common. The high frequency of adverse and toxic reactions may be in part related to the average older age of patients with enterococcal IE (mean age 60 years) than that of patients with IE caused by other microorganisms (mean age 40 to 55 years).⁷⁸ Vestibular disturbances occurred in 10 to 30% of patients treated with streptomycin and 13 of 16 patients (81%) treated with gentamicin had abnormal values for serum creatinine. Wilkowski and associates (unpublished data) report that ototoxic reactions may also occur with the use of ampicillin and gentamicin. Serum concentration of aminoglycosides and vancomycin should be measured frequently throughout the course of treatment. Peak serum concentration of streptomycin 1 hour after administration of the dose should be adjusted to 10 to 15 µg/ml and should not exceed 20 µg/ml. Peak 1 hour serum concentration of gentamicin should range from 3 to 5 µg/ml. Peak 1 hour serum concentration of vancomycin should not exceed 20 µg/ml.

Penicillin sensitive staphylococcal IE (MIC ≤ 0.1 µg/ml)

The course of IE caused by staphylococci is often acute and immediate antimicrobial therapy is required. Staphylococcal endocarditis should be suspected in illicit intravenous drug abusers, patients with prosthetic heart valves, and when the suspected portal of entry is cutaneous or is associated with intravenous catheters. Because more than 50% of community acquired and more than 80% of hospital acquired staphylococci produce penicillinase, initial treatment of suspected staphylococcal IE should include a penicillinase resistant penicillin or a cephalosporin.

Table V Treatment of penicillin resistant staphylococcal infective endocarditis (MIC ≥ 0.1 µg/ml)

| Treatment of methicillin susceptible <i>S. aureus</i> and <i>S. epidermidis</i> infections | |
|--|---|
| Treatment of patients not allergic to penicillin | Alternative treatment of patients allergic to penicillin |
| Nafcillin, oxacillin or methicillin 2 g IV q4h for 4 to 6 weeks | Cephalothin 1 g IV q4h or cefazolin 1 g IV or IM q6h for 4 to 6 weeks or Vancomycin 7.5 mg/kg IV q6h for 4 to 6 weeks |
| Treatment of methicillin resistant <i>S. epidermidis</i> infections | |
| Cephalothin or cefamandole 1 g IV q4h or cefazolin 1 g IV q6h for 4 to 6 weeks | |

Combination use of cephalosporins, vancomycin, gentamicin, rifampin may enhance killing of methicillin resistant *S. epidermidis*.

After the MIC is available, only infections caused by staphylococci with penicillin MIC ≤ 0.1 µg/ml should be treated with penicillin G alone. *S. aureus* strains with penicillin MIC > 0.1 µg/ml usually produce penicillinase and the production of penicillinase can be induced by the presence of penicillin. Table IV outlines the usual therapeutic programs for IE caused by penicillin sensitive staphylococci. A cephalosporin or vancomycin is an acceptable alternative to penicillin in patients who are unable to tolerate penicillin. Treatment should be continued for a minimum of 4 weeks.

Penicillin resistant staphylococcal IE (MIC ≥ 0.1 µg/ml)

Studies have been performed in experimental animals which have compared the efficacy of the most commonly used penicillinase resistant antistaphylococcal agents. Egert and associates⁸⁰ reported that methicillin, nafcillin, and oxacillin were equally effective in experimental rabbit IE. Carrizosa and associates⁸¹ found that methicillin reduced more rapidly than did cefazolin or cephalothin the titers of *S. aureus* in experimental aortic valve vegetations. Cefazolin is more susceptible to inactivation by beta lactamase produced by *S. aureus* than is cephalothin⁸² and some

therapy is effective. We believe that all patients with PVE should receive a minimum of 4 weeks of intravenous therapy with bactericidal antimicrobials.

The use of anticoagulant therapy in patients with IE is controversial. Since the report by Thill and Meyer¹¹ published in 1947 many authorities have affirmed that anticoagulants are contraindicated in cases of endocarditis of natural or prosthetic valves because of the potential risk of central nervous system bleeding after thromboembolism.¹²⁻¹⁴ Because of the increased risk of thromboembolism with discontinuance of anticoagulant therapy in patients with prosthetic valves,¹⁵⁻¹⁷ it would be desirable to continue the use of anticoagulants in patients with PVE provided that such therapy did not increase morbidity and mortality especially from central nervous system bleeding after thromboembolism. We reported earlier¹⁸ that the use of anticoagulants did not increase morbidity or mortality in patients with PVE. On the contrary the risk of major clinical central nervous system complications was increased and the mortality rate was higher when anticoagulants were discontinued. Central nervous system complications occurred nine times more frequently when anticoagulants were discontinued or given in subtherapeutic dosage than when adequate anticoagulation was continued. We believe that carefully controlled anticoagulant therapy should be continued cautiously in patients with PVE. Patients should be observed closely for the development of central nervous system complications. If such complication occurs we agree with Karchmer and associates¹⁹ that use of anticoagulants should be discontinued temporarily. If there is no clinical or laboratory evidence of intracranial hemorrhage anticoagulants may be reinstituted.

Another difference between patients with PVE and those with natural valve IE is the necessity for a more aggressive surgical approach to patients with PVE. We agree with Karchmer and co-workers,²⁰ Richardson and associates²¹ and Saffle and colleagues²² that all patients with PVE who have moderate or severe heart failure that is unresponsive to medical therapy or in whom significant paravalvular leaks develop should undergo valve replacement early in the course of their illness. Failure to act quickly with surgical intervention in these patients significantly increases the mortality rate. The need for early

cardiac valve replacement in all patients with early-onset PVE caused by staphylococci has been stressed by Richardson and associates.²¹

The role of cardiac valve replacement in patients with IE

The role of cardiac valve replacement in patients with PVE and fungal IE has been discussed briefly above. During the analysis of congestive heart failure replaced valves as a leading cause of death among patients with IE and most patients with IE who experience heart failure do so because of hemodynamic consequences of incompetent cardiac valves exacerbated by valvular infection. In a retrospective analysis of patients who underwent cardiac valve replacement because of heart failure caused by IE we found the operative mortality to be directly related to the degree of functional heart failure present at the time of operation. It was compared with a similar group of patients with IE who underwent cardiac valve replacement. Operative mortality was remarkably similar to that of patients with IE when the degree of heart failure was the same at the time of operation in both groups of patients.

In patients with functional Class II heart failure or with sudden-onset severe aortic regurgitation associated with IE, urgent cardiac valve replacement probably offers the only hope for survival. Cardiac valve replacement can be successfully performed in these patients without active infection even when blood cultures are positive in the immediate preoperative period. Procrastination in cardiac valve replacement in these patients in an attempt to establish heart failure by medical therapy or to complete a course of antimicrobial therapy preoperatively usually results in death from cardiac failure. We believe that the hemodynamic status of patients with IE should be the determining factor in timing of cardiac valve replacement rather than the activity of infection or the length of preoperative antimicrobial therapy.

Richardson and associates²¹ suggest that patients with IE due to *S. aureus* should undergo cardiac valve replacement. We agree with Richardson and associates but we do not support that not all patients with IE caused by *S. aureus* require cardiac valve replacement. We experience some patients with IE caused by *S. aureus* especially those with tricuspid regurgitation can be treated successfully with medical therapy.

resistant *S. epidermidis*. The optimal combination of agents would depend on the results of in vitro tests of MBC and SBT and of synergy studies. Until further data are available, infections caused by methicillin-susceptible strains of *S. epidermidis* are probably best treated with a single agent (oxacillin, nafcillin, methicillin, or cephalosporin).

The semisynthetic penicillins and cephalosporins are generally well tolerated, but adverse and toxic reactions occur. Methicillin-associated renal failure and interstitial nephritis have been well documented.^{9, 91} Other adverse reactions associated with the use of semisynthetic penicillins have been granulocytopenia and hepatitis.^{9, 10} Use of a cephalosporin may be associated with neutropenia and occasional renal failure.¹⁰⁸

The mortality rate associated with staphylococcal IE is high. The prognosis among heroin addicts is relatively more favorable than that among nonaddicts.^{9, 10, 10} The mortality rate of taphylococcal IE among nonaddicts usually exceeds 50%.^{9, 17, 109} Poor prognosis has been associated with an age of more than 50 years and the presence of underlying diseases—cardiac disorders, alcoholism, cirrhosis, and diabetes mellitus. The rate of survival from staphylococcal endocarditis is higher if the patient lives long enough to receive at least 2 weeks of antimicrobial therapy.

Treatment of IE caused by other microorganisms

The antimicrobial therapy of IE caused by other microorganisms depends on isolation and identification of the offending organism and the results of in vitro susceptibility tests of MIC, ABC, and SBT. Susceptibility testing may be difficult or impossible with some fastidious gram-negative bacilli, especially *Haemophilus* species. Most *Haemophilus* species are highly susceptible to ampicillin, and IE caused by these microorganisms may be treated successfully with ampicillin administered intravenously for 3 weeks. If in vitro susceptibility tests with this organism cannot be performed, empiric therapy with ampicillin or amoxicillin may be used. Clinical parameters such as disappearance of fever and return of appetite serve as guidelines to the effectiveness of therapy in such cases. Infections caused by microorganisms other than those streptococci, staphy-

lococci, and *Haemophilus* species described above should be treated a minimum of 4 weeks. Most authorities believe that patients with culture-negative IE should be treated with regimens that are effective against enterococcal IE.²

Fungal endocarditis

Candida species and *Aspergillus* species are the most common causes of fungal IE. Of the two, IE due to *Candida* occurs more commonly and is seen most frequently in association with drug addicts.¹ IE caused by *Aspergillus* occurs most often as a complication of cardiac valve replacement.^{10, 9} The course of fungal endocarditis is usually subacute or chronic and is characterized by the frequent occurrence of arterial embolization of large friable fungal vegetations. Treatment of fungal IE with amphotericin B or 5-fluorocytosine or both is frequently unsuccessful, and antifungal therapy combined with cardiac valve replacement is necessary in most cases.⁹

Prosthetic valve endocarditis

During the past 7 years, prosthetic valve endocarditis (PVE) accounted for approximately 17% of the total number of cases of IE seen at the Mayo Clinic. Because of differences in microbiologic causation, expression of clinical syndrome, treatment, and prognosis, patients with PVE should be considered separately from patients with natural valve endocarditis. Infections that occur early (less than 2 months after operation) are most often caused by *S. epidermidis*, *S. aureus*, gram-negative bacilli, or diphtheroids and are associated with a very high mortality rate—more than 80%.¹ Late-onset infections (more than 2 months after operation) are associated with a better prognosis—38% mortality rate in one study—than early-onset infection and are caused by those microorganisms that most often cause natural valve endocarditis.

The antimicrobial therapy of patients with PVE is similar to that of patients with natural valve IE. One major exception, however, is the treatment of patients with penicillin-sensitive streptococcal PVE. These patients should not be treated with short-term intramuscular therapy. In our experience, 4 weeks of intravenous aqueous penicillin G (20 million units per day) for 4 weeks combined with streptomycin (75 mg/kg intramuscularly every 12 hours for the first 2 weeks of

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ment alone. These patients should be followed closely and if heart failure or other signs of hemodynamic deterioration appear, consideration should be given to urgent cardiac valve replacement.

In general, the same guidelines for cardiac valve replacement in the usual population apply to drug addicts. A special situation exists in drug addicts who have recurrent infection of the tricuspid valve with gram-negative bacilli that are resistant to multiple drugs, notably *Serratia marcescens* and *Pseudomonas* species. In these cases, excision of the tricuspid valve without immediate artificial valve replacement may be necessary.¹³ Although progressive right-sided heart failure may subsequently develop in these patients, some patients have tolerated the absence of a tricuspid valve for a surprisingly long time.

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stellate ganglionectomy preceding an experimental coronary occlusion reduced the incidence of acute cardiac deaths, indeed, in two groups of ten dogs each ventricular fibrillation occurred in five neurally intact animals but in only one previously sympathectomized dog. In addition the authors advanced the remarkable hypothesis that the nervous pathways which carry the painful impulses in angina may perhaps act as a reflex arc which carries pain and other impulses to the heart which are deleterious to its function. A recent and appreciable review⁸ pointed out that Cox and Robertson's data if analyzed according to current criteria fail to attain statistical significance. Had those authors known the future fashion of a p value they would have certainly performed two more experiments for the sake of a p value < 0.05 .

Myocardial ischemia and autonomic disturbance The work by Pantridge's group⁹⁻¹⁰ represents a clinical milestone. It was found that the vast majority of patients had signs of autonomic disturbance within the first 30 minutes from the onset of acute myocardial infarction, signs of excessive sympathetic activity were more frequent in cases of anterior infarction whereas signs of vagal overactivity were more frequent in inferior infarctions. Thus it was suggested that different specific mechanisms likely to be neural were involved in either anterior or inferior infarctions independently of common denominators such as pain, emotion or pump failure.

a. Increased efferent sympathetic activity Classically an increased sympathetic activity in the course of a visceral disease is thought to result from brain mechanisms like pain and emotion or from peripheral reflex influences.

The work by Littler and associates¹¹ on direct arterial pressure and electrocardiograms recorded in ambulatory patients with angina pectoris showed that electrocardiographic changes typical of ischemic attacks can be accompanied by hypertension and tachycardia before the onset of pain. The literature associating angina and increases in arterial pressure and heart rate is extremely abundant; however the novelty of that report was that pressor events were independent of emotion and pain and therefore the most likely cause was a pressor reflex from the heart. This hemodynamic picture has been particularly well documented in the more recent studies by Maseri's group.¹²

There is increasing evidence that excitatory afferent fibers from the heart traveling in the cardiac sympathetic nerves may have an important role in determining the reflex sympathetic activity returning to the heart and affecting cardiac events: these reflexes can be properly defined as cardio-cardiac sympathetic reflexes.¹³⁻¹⁶ The excitation of cardiac sympathetic afferent fibers is also capable of reflexly inhibiting the activity of efferent vagal cardiac fibers through a sympatho-vagal reflex.¹ Thus the excitation of sympathetic cardiac afferent fibers could affect the heart and stimulate its function through an increased sympathetic discharge: a synergistically reduced vagal restraint.

Cardiac sympathetic sensor endings, i.e., myelinated¹⁷ or unmyelinated fibers¹⁸ are mechanoreceptors normally excited by mechanical events¹⁹⁻²⁰ but their activity can be further enhanced by chemical substances like bradykinin²¹ which are known to be released in the ischemic heart. The hypothesis is that mechanical abnormalities of the ischemic myocardium are chemical factors possibly in sequence under crescendo excitation of spontaneously active sympathetic afferent fibers leading to pressor reflexes and above a given threshold to pain. When pain supervenes in the course of a clinical ischemic episode a further rise in arterial pressure usually occurs.¹³⁻¹⁵

Thus sympathetic overactivity could have principle opposite consequences. On the one hand it might beneficially attempt to maintain normal ventricular function through an increase in contractility²² thus opposing ventricular dilation and vagally mediated depressor reflexes. On the other hand deleterious effects are fully suggested by numerous facts. The traditional view is that an increased sympathetic activity profoundly alters the balance between oxygen supply and demand especially in the exposed myocardium. In electrophysiological terms it would increase the electrical inhomogeneity which already results from cellular damage through mechanisms of altered automaticity and dispersion of the refractory period.

That sympathetic cardio-cardiac reflex influence occurrence in arrhythmias in the ischemic heart has recently been demonstrated in experimental animals. The interruption of afferent sympathetic limb of the cardio-cardiac reflex by a section of dorsal roots from the cervical

Neural mechanisms in life threatening

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Arrhythmias may be due to abnormalities of automaticity of conduction or to a combination of both. The visceral nervous system through its sympathetic and parasympathetic outflows can modify both of these properties and quite complex interactions are likely to occur.

Disturbances in cardiac rhythm are quite common but there is a major difference between benign and life threatening arrhythmias.

It is currently held^{1,2} that any condition increasing the electrical inhomogeneity of cardiac muscle renders it more vulnerable to arrhythmic mechanisms including the autonomic influences. Indeed it seems likely that some electrical inhomogeneity should be necessary either originating in the myocardium itself or due to inhomogeneity in the influences playing upon it to create those conditions usually associated with life threatening arrhythmias.

It is the purpose of this brief review to analyze some clinical and pathophysiological states often characterized by lethal arrhythmias and in which autonomic mechanisms seem to play a major role. Its role in the different conditions is likely to range from what seems to be an aggravating factor as occurs during acute myocardial ischemia to what seems to constitute a more substantial pathogenetic mechanism or at least a crucial trigger as in the case of the long QT syndrome. In this review the underlying cellular electro-

physiology will be only alluded to while emphasis will be placed on the overall autonomic influences in an attempt to analyze the genesis of their changes and the role of their effects in the occurrence of life threatening arrhythmias. On the basis of this analysis we shall also advance some logical therapeutic implications.

1 Neural mechanisms in arrhythmias associated with myocardial ischemia

It was the merit of surgeons to have first appreciated that some crucial interaction could occur between myocardial ischemia and the nervous system to cause lethal arrhythmias. Indeed this concept happened to develop during the attempts at solving another problem that of the relief of anginal pain. Apparently François Franck in 1899 proposed a cervico-thoracic sympathectomy for the interruption of the nociceptive path from the heart (quoted by Danielopolu³).

In 1916 Jonnesco followed that suggested but the intervention was judged physiologiquement inadmissible by Danielopolu⁴ as in his opinion it would also interrupt the efferent cardiac sympathetic supply thought to be a vasodilator of the coronary arteries thus enhancing the risk of coronary spasm then as fashionable as nowadays. Lenche and co-workers shared for some years Danielopolu's view but eventually felt as a result of both clinical and experimental work that a high thoracic sympathectomy could be beneficial in cases of angina pectoris as such a procedure seemed to attenuate the tendency to ventricular fibrillation.

A few years later in 1936 Cox and Robertson stressed again on much better grounds that

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arrhythmias are the experiments performed by Verner Lown and their associates²⁹⁻³². They found that hypothalamic stimulation not only promotes fibrillation in animals with acute myocardial ischemia²⁹ but also lowers the threshold for ventricular fibrillation in intact animals³⁰. These effects on ventricular vulnerability could be obtained in vagotomized animals independently of changes in heart rate or in blood pressure, thus they were mediated by changes in sympathetic activity.

Electrical stimulation applied directly to the nerves going to the heart has also yielded a considerable amount of information. Stimulation of the stellate ganglia lowers the threshold for ventricular fibrillation, decreases ventricular refractoriness, and may produce ventricular arrhythmias.

However, information obtained using the technique of electrical stimulation, although valuable in identifying neural circuits and in showing the effects of a massive activation of nerve fibers present in the stimulated nerves should be interpreted with caution because of the artificial nature of the stimulus. A useful way to integrate these notions is to study the effects of denervation which explores the importance of the continuous neural activity of vagal and sympathetic nerves. This goal was initially achieved by studying the effects of bilateral stellectomy, recently also unilateral stellectomy has been employed with partly unexpected results. For instance, among other effects, bilateral stellectomy increases the threshold for ventricular fibrillation, on the other hand, while left stellectomy is attended by a major increase in the ventricular fibrillation threshold, right stellectomy paradoxically results in a striking fall in the threshold.³³ The antiarrhythmic effect of left stellectomy has potentially profound clinical implications and will be further discussed in the section on therapy. The paradoxical arrhythmogenic effects of right stellectomy have been now repeatedly confirmed in several experimental conditions.

The role of vagal activity in ventricular arrhythmogenesis is still unclear. The traditional view that the vagus exerts little or no influence on ventricular electrical properties was initially challenged by Kent and Epstein, who found that vagal stimulation significantly increased the threshold for ventricular fibrillation in both the

normal and the ischemic myocardium. Subsequently Verner and associates³⁴ found that activation exerts a protective effect and sympathetic activity is elevated and is without effect when the adrenergic input to the heart is largely prevented by beta adrenergic blockade. A possible basis for this effect would be represented by an activation of cardiac presynaptic receptors modulating the release of catecholamines. The most likely anatomic site for the interaction is the His-Purkinje system³⁵ which is richly innervated by vagal sympathetic neuroeffector endings. The cellular basis for this adrenergic-cholinergic mechanism has recently been indicated by Watanabe and Besch³⁶ as possibly being mediated by AMP cyclic GMP interactions.

However, a correct understanding of the vagal effects on arrhythmias is made difficult by the fact that changes in vagal activity are accompanied by profound changes in heart rate, a very important influence on ventricular arrhythmias. For instance, the suggestion that phenylephrine induced suppression of ventricular arrhythmias depends upon the reflexly mediated increase in vagal activity is not supported by a recent study. Indeed Weiss and colleagues³⁷ using atrial pacing have shown that the arrhythmic effect of phenylephrine is mostly due to the attendant slowing in heart rate.

In the next paragraphs sympathetic and arrhythmogenic influences will be reviewed occurring in the following conditions: (1) psychological stress, (2) exercise, and (3) sleep. The long QT syndrome will then be considered as a peculiar condition in which neural mechanisms lead to lethal arrhythmias.

1 Psychological stress The relationship between psychological factors, cardiac arrhythmias, and sudden death has been dealt with in two reviews^{38,39} we will only discuss here the evidence that the critical link for this relationship is represented by the sympathetic nervous system.

There is abundant clinical literature of anecdotal type showing the occurrence of cardiac arrhythmias and even sudden death during emotionally important events. However, the evidence comes, as is often the case from experimental studies.

Verner Lown and their associates⁴⁰ have studied the effect of a psychologically stressful environment

cervical segment to the fifth thoracic segment was capable of reducing the number of ectopic beats associated with short lasting coronary occlusion²²

From a clinical point of view it is important to mention the high incidence of ventricular tachyarrhythmias in patients with anterior myocardial infarctions as was shown by Pantridge's group⁹

b Increased efferent vagal activity As was first shown by Pantridge's group soon after inferior myocardial infarction there is a very high incidence of bradycardia or hypotension or both which often seems to act as a prelude to ventricular fibrillation. Likewise during transient episodes with electrocardiographic signs of myocardial ischemia accompanied by pain or not hypotension and bradycardia can occur or hypotension alone can occur without the tachycardia expected from baroreflex deactivation²³

The laboratory notion of vagally mediated depressor reflexes from the heart is an old one deriving from the experiments with veratrum alkaloids of von Bezold and Hirt. It was not until a hundred years later however that depressor reflexes with vagal afferent fibers were studied adequately with respect to their possible pathophysiological role during experimental coronary occlusion²⁴ distension of cardiac chambers and increase in coronary pressure

These depressor reflexes act through the excitation of the vagal and the inhibition of the sympathetic outflow. However what appears as a dangerous clinical reality does not easily fit in the simple scheme provided by some laboratory findings indicating that an increased vagal activity reaching the heart especially if associated with a reduction of sympathetic tone should increase electrical stability and raise the fibrillation threshold²⁵. However the antiarrhythmic effects of the vagus may be augmented or reversed by its profound influence on heart rate in the setting of acute myocardial ischemia²⁶

c The sympatho vagal interaction Administration of atropine for management of bradycardia has been reported to often unmask a simultaneous sympathetic overactivity. This is indeed not surprising. The left ventricle has a rich sensory innervation with afferent fibers running both in the vagi and in the sympathetic nerves. A mechanical abnormal event with or without the sensitizing contribution of chemical substances

has the potentiality of eliciting the following set of reflexes: sympatho sympathetic; sympatho vagal; vago vagal and vago sympathetic. Which of these reflexes will prevail will depend on the type of sensory endings excited on the specific nature and location of the abnormal stimulus and on the complex integrating connections in the brain.

Yet a frequent pathophysiologic event could be that of an increased vagal and sympathetic efferent activity as the result of prevailing vago vagal and sympatho sympathetic reflexes. Such a common event would weaken the old conception of vagal and sympathetic outflows working in a sort of reciprocal arrangement. Bergamaschi²⁷ has recently shown that after ligation of the anterior descending coronary artery the simultaneous stimulation of cardiac vagal and sympathetic efferent fibers produced a greater incidence of severe arrhythmias including ventricular fibrillation than the separate stimulation of either efferent system.

2 Neural mechanisms in arrhythmias not associated with myocardial ischemia

There is a definite experimental proof that sympathetic and vagal activities can also elicit arrhythmias in the absence of any demonstrable degree of myocardial ischemia. The sympathetic and vagal arrhythmogenic effects have been studied primarily by stimulating or interrupting the neural paths to the heart or by injecting various drugs that interfere with autonomic activity.

Electrical stimulation of various areas of the brain has resulted in a diversity of cardiac arrhythmias²⁸⁻³⁰ mostly mediated by activation of the sympathetic nervous system. Manning and Cotten³¹ showed that the simultaneous increase in both sympathetic and vagal activity was particularly detrimental. These arrhythmias occur during stimulation and after cessation of the stimulation. Evans and Gillis³² have concluded that arrhythmias produced during the stimulation are predominantly mediated by the sympathetic nerves while the others are primarily dependent upon a vagal reflex discharge. Arrhythmias and electrocardiographic changes induced by brain stimulation may represent an interesting model for arrhythmias and repolarization abnormalities often accompanying cerebrovascular accidents.³³

Relevant to the problem of life threatening

ischemic myocardium may precipitate arrhythmias. In particular the rebound of REM sleep which occurs as a consequence of REM sleep deprivation or after withdrawal of drugs such as barbiturates may be quite arrhythmogenic in an ischemic heart.⁷

On the other hand there is evidence that quiet sleep may represent a state of even greater risk. During quiet sleep the QT interval is prolonged as compared to REM sleep^{13,14} vulnerability to arrhythmias in hypoxic kittens increases¹⁵ and ventricular fibrillation is more rapidly induced by acute ischemia in pigs.¹⁶ Skinner and co-workers¹⁷ have also shown that pigs with an acute myocardial infarction have more cardiac arrhythmias during sleep as compared to their awake state.

Another important clinical condition (8 000 to 10 000 victims per year in the US) in which lethal cardiac arrhythmias may occur during sleep is the Sudden Infant Death Syndrome. The typical clinical story is that of a healthy infant age two to four months put to sleep for a nap or for the night and found dead shortly thereafter or the next morning. Although the cause or more probably the causes of these sudden deaths have not been clarified the possibility has recently been proposed that at least some cases of Sudden Infant Death Syndrome might depend upon an abrupt sympathetic discharge taking place through an asymmetrically developed sympathetic innervation of the heart with dominance of left sided nerves.

The long QT syndrome. The idiopathic long QT syndrome (LQTS) is characterized by prolongation of the QT interval frequent alternation of the T wave and syncopal episodes due to ventricular fibrillation eventually resulting in the sudden death of most affected individuals.¹⁸ Crucial for the understanding of the pathogenetic mechanisms is the clinical observation that the syncopal episodes almost always follow an emotional or a physical stress. This tight association between emotions such as fear or anger and ventricular fibrillation undoubtedly contributes to the uniqueness of this clinical entity.

A most likely pathogenetic mechanism suggested by clinical and experimental data is a congenital imbalance between right and left cardiac sympathetic innervation with a left dominance. Alternatively it is likely the basic defect may be an unknown cardiac abnormality

decreasing electrical stability and sensitivity of the myocardium to sympathetic discharges. In any case, there is no doubt that the ventricular tachyarrhythmias which lead the LQTS patients to death depend upon sudden increases in sympathetic activity mostly through the dominant left stellate ganglion.

Data regarding the pathogenesis of the LQTS syndrome have been gathered mostly by manipulation of the sympathetic nervous system. In experimental animals right stellectomy or transection of the sympathetic nerves results in (1) prolongation of the QT interval^{19,20} (2) increase in ventricular arrhythmias during myocardial ischemia,²¹ or case "and emotion"²² (3) lowering of the threshold for ventricular fibrillation and (4) increase in ventricular excitability.²³ Furthermore patients with the long QT syndrome alternate the T wave has been elicited by blockade of the right stellate ganglion²⁴ and has been suppressed by blocking the left stellate ganglion.²⁵ Alteration of the T wave and ventricular arrhythmias have been produced in animals²⁶ and in man²⁷ by stimulation of the left stellate ganglion.

The understanding of the mechanisms triggering ventricular fibrillation has dictated a therapeutic approach to the long QT syndrome: beta adrenergic blocking agents or left stellectomy. The most recent evaluation of the effectiveness of therapy in the long QT syndrome indicates that in over 500 patients beta blockers reduce the mortality rate from 78% (untreated patients) to 6%. At the present time left stellectomy was performed the first time in 1970 by Moss and McDonald.²⁸ has been performed in 20 patients all refractory to beta blockers resulting in the suppression of complete or almost complete of the syncopal attacks. With other therapies the mortality rate is still around 50%. The available data indicate that the first choice treatment is represented by beta blockers at full dose should however syncopal attacks continue left stellectomy becomes mandatory.

3 Therapeutic implications

Attempts to reduce the incidence of life-threatening arrhythmias in patients at high risk of sudden cardiac death should be directed against those factors which may induce or increase cardiac electrical instability. The overall approach

ment Dogs were exposed to two different environments a cage in which the animals were left undisturbed and a sling in which they received a transthoracic shock for three consecutive days On days 4 and 5 the effects of the two environments were compared, as the dogs entered the sling they became restless exhibited somatic tremor and their heart rate increased markedly Under this condition it was found that the threshold for repetitive extrasystoles which was considered as a marker of cardiac vulnerability was reduced by 50% That this increase in vulnerability was mediated by the sympathetic nervous system was indicated by the fact that it was completely prevented by a beta adrenergic blocking drug³⁸ Furthermore when dogs with a recent myocardial infarction and free of arrhythmias were reexposed to the aversive environment ventricular arrhythmias including ventricular tachycardia occurred these phenomena disappeared when the animals were returned to the quiet

Another hint as to the arrhythmogenic role of stress comes from the observation⁴⁰ that farm pigs sufficiently adapted to the laboratory are less prone to ventricular fibrillation after coronary occlusion In this case however beta blockade with propranolol did not afford any protection The possibility has been raised⁴¹ that in this study blockade of beta adrenergic cardiac innervation was inadequate

2 Exercise Exercise can increase the incidence of ventricular arrhythmias not only in patients with coronary heart disease but also in normal subjects⁴ Most of these arrhythmias occur in the post exercise recovery period

It is common knowledge that during exercise there are a simultaneous increase in sympathetic activity and a withdrawal of vagal tone upon cessation of exercise vagal activity immediately resumes while the cardiac effects of catecholamines are still present

Three recent studies have provided evidence on the relationship between the sympathetic nervous system and exercise induced cardiac arrhythmias In dogs performing submaximal exercise on a treadmill some arrhythmias occurred in a small percentage of intact animals and in an equally percentage of animals with left stellectomy arrhythmias were absent after bilateral stellectomy However they were markedly increased after

right stellectomy with the left stellate ganglion intact⁴² In another study in dogs whose hearts were completely denervated with the exception of the ventrolateral cardiac nerve which originates from the left stellate ganglion arrhythmias were often produced by exercise⁴³ Likewise in 75 patients who had undergone unilateral or bilateral stellectomy as a treatment of Raynaud's syndrome and who were studied with submaximal exercise on a treadmill⁴⁴ exercise induced ventricular arrhythmias appeared in a very small percentage of control subjects with intact stellate ganglia and in patients with left stellectomy These arrhythmias were entirely absent in patients who had a bilateral stellectomy and occurred in a considerable proportion of patients with right stellectomy These studies have shown the important role of cardiac sympathetic nerves in the genesis of arrhythmias during exercise and have indicated the particular arrhythmogenic potential of left sided sympathetic nerves especially when a condition of sympathetic imbalance is created

Another mechanism potentially relevant for the development of arrhythmias during exercise in patients with coronary heart disease is represented by the fact that during exercise coronary flow is still restricted by sympathetic vasoconstrictor tone and that this tonic vasoconstriction is dependent upon nerve fibers passing through the left stellate ganglion Indeed after left stellectomy coronary flow during exercise is higher compared to control condition⁴⁵ suggesting that the sympathetic activity may limit the vasodilation of the coronary bed secondary to increased metabolic demands

3 Sleep The effect of sleep on cardiac arrhythmias is still controversial Clinical findings ranged from a complete abolition or an amelioration of cardiac arrhythmias during sleep⁴⁶ to an exclusive occurrence of arrhythmias during sleep⁴⁷

REM sleep because of its association with bursts of autonomic activity⁴⁸ has been considered for a while the stage of sleep in which the heart is most vulnerable Transient elevations in blood pressure and heart rate occur during REM sleep⁴⁹ suggesting that sympathetic bursts may be superimposed on the tonic decrease in sympathetic activity⁵⁰ These changes may decrease the electrical stability of the heart and in an

ischemic myocardium may precipitate arrhythmias. In particular, the rebound of REM sleep which occurs as a consequence of REM sleep deprivation or after withdrawal of drugs such as barbiturates may be quite arrhythmogenic in an ischemic heart.⁷²

On the other hand, there is evidence that quiet sleep may represent a state of even greater risk. During quiet sleep the QT interval is prolonged as compared to REM sleep,^{73,74} vulnerability to arrhythmias in hypoxic kittens increases,⁷⁵ and ventricular fibrillation is more rapidly induced by acute ischemia in pigs.⁷⁶ Skinner and co-workers⁷⁷ have also shown that pigs with an acute myocardial infarction have more cardiac arrhythmias during sleep as compared to their awake state.

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3 Therapeutic implications

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dence pointing to the crucial role of the cardiac innervation as the precipitating factor implies that measures which prevent or antagonize sympathetic or parasympathetic effects might prove beneficial.

Beta adrenergic blocking drugs have gained wide clinical acceptance as antiarrhythmic agents. Along the same line of thought surgical ablation of the cardiac sympathetics has recently been suggested as a possible therapeutic procedure. Both approaches will be briefly reviewed. Finally the possibility will be considered of pharmacological blockade of parasympathetic efferent activity.

1 Beta adrenergic blocking agents That beta adrenergic blocking agents may be effective in treating or preventing life threatening arrhythmias in coronary patients is suggested by animal experiments which show that these agents seem to reduce the number of ventricular dysrhythmias resulting from coronary occlusion.¹

The effectiveness of these compounds in clinical dysrhythmias is incompletely documented however. Taggart and colleagues² by monitoring the electrocardiogram for prolonged time in subjects performing their daily tasks have observed that beta blockade is highly effective in protecting against emotionally induced arrhythmias in both normal subjects and in patients with coronary heart disease. Yet the clinical condition in which prompt administration of beta adrenergic antagonists may in principle be most advantageous acute myocardial infarction with dysrhythmias generally requires urgent therapeutic measures thus precluding studies which satisfy the stringent rules of clinical trials. The majority of investigators³⁻⁵ who have tried intravenous administration of various beta blockers in patients with acute myocardial infarction have found that no more than 50% of patients treated responded favorably; the drugs being most effective in sinus tachycardia and ventricular premature beats and least effective for reversing atrial fibrillation. It is worth emphasizing furthermore that the benefit risk balance of administering a beta blocker to patients under such a dangerous condition as acute myocardial infarction is always difficult to predict and to assess the outcome in the individual case will largely depend on the net balance between further depression of sympathetic dependent cardiac contractility on

one side and an improvement in pumping function and decreased risk of ventricular fibrillation by reversion of tachyarrhythmias on the other side.

It should also be considered in view of the evidence summarized previously suggesting that dysrhythmias in early myocardial infarction may be mediated by either the cardiac sympathetics or the vagi according to the infarction site (anterior versus inferior) that more definite advantages may be obtained by limiting the use of beta blockade to patients with anterior myocardial infarction.

A further application of beta blockers which lends itself to a better though extremely laborious testing is in preventing sudden death and the recurrence of cardiac events when given over the long term following myocardial infarction. A few trials recently completed⁶⁻⁸ have shown favorable results of the long term administration of the beta adrenergic blocking agents alprenolol and practolol. The practolol study^{6,7} indicated that the protective effect of the drug consisting in a significant reduction of overall mortality rate and in sudden death was most consistent in those patients whose original infarcts were localized anteriorly again a clear reference to Pantridge's work. Because of the severe side effects of practolol continuation of its favorable results is being sought in other trials presently under way and by using other beta blockers.

The striking favorable effects of beta blocking therapy in preventing lethal arrhythmias in the long QT syndrome^{9,10} have already been summarized in the preceding section.

2 Left sympathectomy An alternative procedure for preventing or limiting sympathetic arrhythmogenic influences upon the heart is represented by cardiac sympathectomy. Evidence from animal experiments that we have summarized above clearly shows that the following beneficial results can be obtained even when cardiac sympathectomy is limited to the left side and only consists in left stellectomy. Indeed left stellectomy reduces the incidence of ventricular arrhythmias associated with short lasting coronary occlusion. It produces a marked increase in the threshold for ventricular fibrillation¹¹ it prolongs the ventricular refractory period¹² it increases the capability of the coronary bed to dilate¹³ it does not reduce cardiac performance during exer-

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influences an approach that has been neglected for years perhaps as a consequence of the dominant role played by the so called pump physiology in the traditional approach to cardiovascular disease

This new approach is already reflected in useful therapeutic measures to correct life threatening arrhythmias both in frequently occurring cases of cardiac ischemia and in the rarer conditions in which ischemia is absent it represents the rationale of current promising attempts to provide prevention of myocardial infarction and sudden death Hopefully it will stimulate further research which may lead to more sophisticated and improved therapeutic strategies in the near future

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Clinical pathologic conference

Perioperative hypertensive crisis and hemorrhagic diathesis Fatal complication of clinically unsuspected pheochromocytoma

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Case presentation

Dr Olney The patient a 77 year old woman was first seen at the Mayo Clinic on November 30 1977 with a six month illness characterized chiefly by malaise fatigue anorexia weight loss and fever. Her previous medical history included central retinal vein occlusion in 1976 hypertension of ten years duration a heart murmur known for 20+ years and hysterectomy oophorectomy in 1956. She was currently taking Dyazide one capsule per day for her hypertension.

During the preceding six months she had consulted several local physicians and was given a variety of tentative diagnoses for her illness including upper respiratory infection pneumonia pulmonary edema and urinary infection. Documentation of these diagnoses was lacking and therapies directed at the conditions failed to appreciably alter her apparently deteriorating well being. The physical findings described at various times during this period included blood pressure recording ranging from 110/70 to 190/80 mm Hg and a grade 2/6 systolic ejection murmur. Some of the laboratory test results were a white blood cell count of 16,200/cu mm sedimentation rate 40 mm/hr Westergren blood glucose 150 to 212 mg/dl normal urinalyses and normal chest roentgenogram.

On November 30 1977, she was taken to

Rochester Methodist Hospital. By this time she was recorded as having had a 20 kilogram weight loss. She suffered from a constant cough with some production of dark brown sputum. Her medical history included five or six "spells" over the preceding three months characterized by vertigo and tachycardia of 10 to 15 minutes duration followed by somnolence for 4 to 5 hours. There was some question of loss of consciousness at these times but this was not certain.

On physical examination her blood pressure was 120/65 mm Hg and her body temperature was 37.2° C on admission. She had a fine tremor of the hands and tongue. Her lungs were clear on auscultation. The apex impulse was palpable 1 cm lateral to the midclavicular line with a parasternal lift described. A grade 3/6 systolic murmur was present at the base of the heart with radiation to the carotid arteries and the apex. This was considered to be a left ventricular outflow murmur. Neither gallop rhythm nor diastolic murmur were audible.

On the evening of the first hospital day her temperature rose to 39.4° C. Blood cultures drawn on this day were later reported to be positive for a gram positive coccus. A total of nine blood cultures were drawn during her first two hospital days and they were all positive for the organism which was further identified as *S. botrytis*.

Some of the initial evaluation included 11.5 g/dl white blood cells with 72% neutrophils and a platelet count of 151,000/cu mm. 10.6 second serum sodium potassium 4.3 mEq/L.

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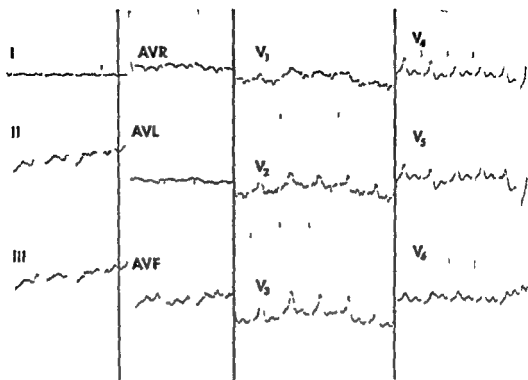


Fig 2 Admission electrocardiogram of November 30 1977 showing sinus tachycardia at the rate of 130 per minute and minor non-specific ST T wave changes

vegetations on the left coronary and noncoronary valve cusps. The aortic valve was replaced with a Bjork Shiley prosthesis. At the completion of the surgery bleeding difficulties were encountered with hemodynamic instability. Hemostasis was eventually achieved and she was treated with intravenous infusion of sodium nitroprusside because the systolic blood pressure had abruptly risen to 280 mm Hg. Following this her systolic blood pressure fell transiently to 60 mm Hg before a more even control was achieved.

In the early postoperative hours the patient had further bleeding problems from the surgical site necessitating a reoperation to secure hemostasis. Her prothrombin time, activated partial thromboplastin time and fibrin split products were now elevated and the plasma fibrinogen was low. She was deeply comatose throughout the immediate postoperative period and she died the next day.

Clinical discussion

DR SPITTELL: To recapitulate what has been outlined in the case presentation, the patient was an elderly woman who came here with a six-month illness characterized by malaise, fatigue, anorexia, weight loss, and fever, all fairly nonspe-

cific symptoms. She had a past medical history that included hypertension of 10 years duration and a heart murmur for 20 years. You will note that prior to being seen here she had been managed as having had pneumonia but full documentation of this diagnosis was lacking. Her laboratory studies included a sedimentation rate which was in a never-never land of 40 mm/hr. I would call your attention to her fasting blood glucose of 150 to 212 mg/dl and her blood pressure which ranged from 110/70 to 190/90 mm Hg in her past workups. By the time she arrived here on November 30, she had had a 90-lb weight loss in the preceding six months. Also noted were a couple of spells characterized by some vertigo and tachycardia followed by syncope and possibly by loss of consciousness. Our physical findings were as recorded and you will note that she had a grade 3/6 systolic murmur.

The patient had fever during her initial day of hospitalization. The growth of *Streptococcus* from multiple blood cultures is worth spending a few minutes discussing. *Streptococcus* is a group D nonenterococcal streptococcus and there was a recent report by Klem and colleagues describing some unusual associations of infections by this particular organism. These

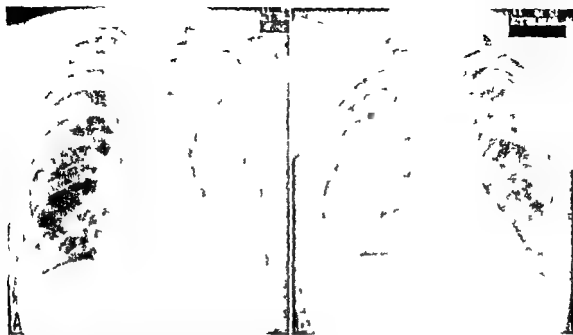


Fig 1 A Admission chest roentgenogram of November 30, 1977, showing a normal cardiac silhouette and pulmonary vascularity. B Preoperative chest roentgenogram of December 15, 1977, showing increased pulmonary vascular markings and changes consistent with interstitial edema.

blood creatinine 1.3 mg/dl; fasting blood glucose 100 mg/dl; serum glutamic oxaloacetic transaminase 27 U/L (normal 8 to 20 U/L); serum bilirubin 0.6 mg/dl; total thyroxine 4.2 μ g/100 ml (normal 5 to 13.5 μ g/100 ml); syphilis serology nonreactive; antinuclear antibody negative; and serum iron 33 μ g/dl (normal 60 to 180 μ g/dl) with total iron binding capacity of 10% saturation (normal 18% to 50%). Serum albumin was slightly increased and gamma globulin was slightly decreased. The fungal and brucella blood cultures, acid fast smears, sputum cytology, and urine cultures were all negative. An intermediate tuberculin skin test showed 10 mm of induration. An excretory urogram was normal and the admission chest roentgenogram (Fig 1A) showed some scattered fibrosis at the lung base and a normal sized cardiac silhouette. An electrocardiogram (Fig 2) showed sinus tachycardia with minimal nonspecific ST-T wave changes. An ear, nose, and throat consultation was obtained regarding the vertigo spells and these were diagnosed as benign positional vertigo. Two separate echocardiograms were done and were interpreted as negative for valvular vegetations, though they did demonstrate evidence of calcium deposits on the aortic valve.

After the initial positive blood culture results, the patient began receiving intravenous aqueous penicillin G 20 million units every 24 hours plus streptomycin 500 mg every 12 hours. When the organism was further identified as *Streptococcus bovis*, the antimicrobial therapy was changed to procaine penicillin 1.2 million units every 8 hours plus streptomycin 500 mg every 12 hours. Despite this antibiotic regimen, the patient continued to have malaise and a low grade daily fever of approximately 38°C.

On the twelfth hospital day, a 3/6 diastolic murmur of aortic insufficiency was heard for the first time. Because the patient's condition continued to deteriorate, aortic valve surgery was contemplated. At that time, two consecutive blood cultures were negative and the white blood cell count was 6,700/cu mm. The prothrombin time, activated partial thromboplastin time, and the plasma fibrinogen were normal. The electrocardiogram was unchanged and the chest roentgenogram (Fig 1B) now showed some interstitial edema. The urinalysis showed 3+ red cells and hemoglobin in the supernatant.

On December 19, 1977, she went to surgery for aortic valve replacement. At operation, the aortic valve was described as calcified with extensive

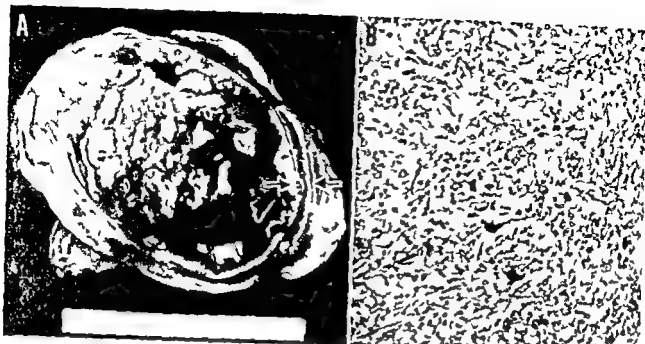


Fig. 4 A Gross appearance of pheochromocytoma attached to the right adrenal gland (arrow). B Photomicrograph of pheochromocytoma (Hematoxylin and eosin stain, original magnification $\times 100$)

murmur. Subsequently, as you note in the case presentation, the patient's condition deteriorated and accordingly, on December 19, she underwent aortic valve replacement. The chest roentgenogram (Fig. 1B) of December 15, four days before surgery, showed changes of pulmonary venous congestion.

At the completion of her surgery, she had difficulties both with bleeding and with hemodynamic instability. The surgeons eventually achieved hemostasis and managed her labile blood pressure with sodium nitroprusside. However, despite a second operation, the patient never really responded and unfortunately succumbed the next day.

We are faced then with a patient who had bacterial endocarditis and her aortic valve replaced, perioperative labile hypertension and hemorrhagic diathesis, and then was comatose following surgery. I think one naturally must consider neurologic complications in this particular context and the paper published by Jones and co-workers from this institution on the neurologic complications of bacterial endocarditis is worth summarizing briefly here. Of 385 patients reviewed, about 15% or 55 had a neurologic complication. Of the total number of patients, about 3% or 11 patients had a documented cerebral hemorrhage. In these 11 cases, the hemorrhage was intracerebral in eight and primarily

subarachnoid in three. The authors concluded that rupture of a mycotic aneurysm was the primary cause for the intracranial hemorrhages in their 11 patients. This would mean that of all the people in their series who experienced cerebrovascular hemorrhage, had mycotic aneurysms as the cause, the incidence of ruptured intracranial mycotic aneurysm in bacterial endocarditis is about 3%.

An advantage of having had the opportunity to review the patient's clinic and hospital records was the chance to read each and every record. The resident who did the admission workup on this patient made the following observations in his initial note: The patient was hypertensive for nine to 10 years; she had spells of vertigo with tachycardia for three months and she had had orthostatic spells for years. In the very last physician's note in the record at the time the patient died, it was recorded that the blood pressure had been ranging widely from 250/160 to 30/0 mm Hg unrelated to any of our measures. This to me was a very telling observation.

I think that there are three diagnostic considerations in this woman in addition to her having had recent bacterial endocarditis. The first is the possibility of an occult colon carcinoma associated with a *Streptococcus bovis* endocarditis. The second consideration is rupture of a cerebral

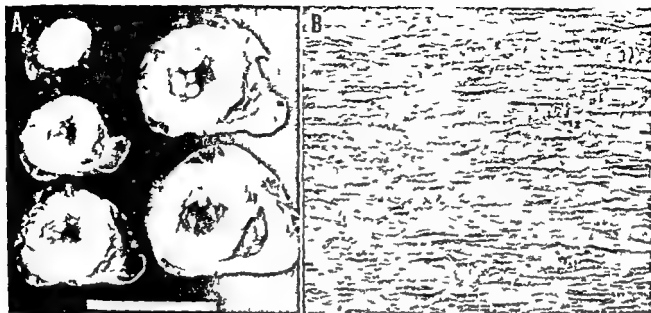


Fig 3 A Gross appearance of five consecutive slices of the transversely sectioned heart showing diffuse epicardial hemorrhage, symmetrical left ventricular hypertrophy, and absence of any old or recent myocardial infarction. B Photomicrograph of subendocardium showing myofibrillar degeneration (Hematoxylin and eosin stain, original magnification $\times 160$).

investigators cultured the fecal flora of 278 subjects made up of seven different groups. There were 105 control patients, 63 patients with carcinoma of the colon, 20 with inflammatory bowel disease, 37 with other gastrointestinal disorders, 12 with histories of previous carcinoma of the colon, 15 patients with recently performed barium enemas, and 21 patients with a noncolonic neoplasm. In some patients cultures were taken from other sites on the body as well. None of those samples from the axillary skin or the vagina showed positive cultures, and only rarely (three of 45) could the organism be isolated from the throat or gingiva. However, on their fecal flora studies 56% of the 63 patients with cancer of the colon cultured *Streptococcus bovis*, a significantly greater incidence of positive cultures for this particular organism than in any of the other patient groups examined. The authors point out further that *Streptococcus bovis* may cause endocarditis almost as frequently as enterococci. Although the association of carcinoma of the colon and infective endocarditis has been reported in only nine patients in at least four and possibly six of those nine patients the microorganism responsible for the endocarditis was *Streptococcus bovis*. They conclude that it is prudent to evaluate patients with *Streptococcus bovis* endo-

carditis for possible carcinoma of the colon. I think this is a very worthwhile piece of information to be brought to your attention.

Proceeding further, we see from the laboratory test results that our patient was anemic; she had a modestly elevated blood creatinine, and her fasting blood glucose was very slightly elevated (100 mg/dl). Her excretory urogram was normal, as was her admission chest roentgenogram (Fig 14). Because the patient described episodes of vertigo, the ear, nose, and throat service was asked to see her in consultation, and after their examination they concluded that she had benign positional vertigo.

The original cardiovascular consultant who saw this woman noted that she had been sick for six months; she had a heart murmur, she was anemic, and she had had fever and weight loss. He considered the possibility of bacterial endocarditis but he was concerned because, in spite of her having had this illness for six months, she did not have an aortic insufficiency murmur. Two echocardiograms were done but did not really help in the diagnosis, nor in the identification of valvular vegetations. Nonetheless, after the results of the blood cultures were reported, a therapeutic antibiotic regimen was instituted. Then, finally, 12 days later, the first observer noted a diastolic

made through workups of hypertension in eight patients as an incidental finding at laparotomy for an unrelated condition in four patients and because of the associated endocrinopathy in one patient. Of the 41 patients with clinically unsuspected pheochromocytoma, death was directly or indirectly related to the tumor and its complications in 30 patients—11 had intraoperative hypertensive or hypotensive crisis, 11 had cardiac failure, seven had cerebral hemorrhage, and one had metastases.⁴

Unexpected postanesthetic death and death during surgical procedures for unrelated conditions are well known complications of unsuspected pheochromocytoma.⁵⁻⁷ The surgical procedure may be a simple one such as the incision of an infected finger pulp or a breast biopsy.⁸ Pheochromocytoma is a true great mimic; its clinical manifestations may be kaleidoscopic or minimal.⁹ Effective biochemical tests for the detection of pheochromocytoma are available.¹⁰ However, a high index of suspicion is a prerequisite for the clinical diagnosis of pheochromocytoma. If diagnosed, it is curable in about 90% of patients but will eventually be lethal in almost all cases if untreated.¹¹ Think of it, confirm it, find it, and remove it—remains sound advice.

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mycotic aneurysm which of the possibilities that I entertained would statistically be the most likely. The third consideration is a pheochromocytoma that had not been recognized. While the latter is quite rare or considerably more rare than a mycotic aneurysm, everything in this patient's story is compatible with that diagnosis. This is because of the observations that were recorded in the last physician's note in the record of this patient and because of her spells, her orthostatic symptoms and her past history of labile hypertension.

Dr Spittell's Clinical Diagnoses

- 1 Recent bacterial (*Streptococcus botis*) endocarditis of the aortic valve
- 2 Recent aortic valve replacement
- 3 Perioperative cerebrovascular hemorrhage secondary to ruptured mycotic aneurysm. To be ruled out are the possibilities of an unrecognized pheochromocytoma and coincidental carcinoma of the colon.

Pathologic discussion

DR LIE: The autopsy was performed within 8 hours of death. The immediate cause of death was indeed a cerebrovascular catastrophe. The patient had a subdural hematoma over the right lateral convexity and middle fossa with compression of the right cerebral hemisphere and the rostral brainstem and uncus herniation. There were also secondary hemorrhages in the midbrain and upper pontine tegmentum. There were no cerebral aneurysms ruptured or unruptured.

There was also hemorrhage into the anterior mediastinum (50 ml), the right pleural cavity (800 ml) and the left pleural cavity (100 ml). The heart was enlarged due to left ventricular hypertrophy weighing 680 g and there was a generalized epicardial hemorrhage (Fig 3A). The aortotomy sutures were intact and the aortic valve prosthesis was securely seated. With the exception of a focal 90% atherosclerotic luminal narrowing in the proximal third of the right coronary artery, the extramural coronary arteries showed noncritical (< 75% luminal narrowing) atherosclerosis. Scattered foci of fibrosis were present in the left ventricle. Although there was no regional ischemic necrosis (myocardial infarction) foci of subendocardial myofibrillar degeneration (contraction band necrosis) (Fig 3B) were widespread.

Attached to the right adrenal gland was a large

(8 by 6.5 by 5 cm) well circumscribed hemorrhagic tumor (Fig 4A). This tumor weighed 160 g and histologically was a pheochromocytoma (Fig 4B). A portion of the tumor was freshly frozen at the time of autopsy. Subsequent chemical analyses showed that the tumor contained norepinephrine 21.8 µg/mg, epinephrine 51.2 µg/mg and dopamine 0.3 µg/mg of the wet tissue.

Thus we have an example of the *lethal complication of unsuspected pheochromocytoma* in a patient who had surgery for an unrelated condition, namely *perioperative hypertensive crisis and hemorrhagic diathesis*.

DR SPITTELL: Did the patient have any colonic lesion at all?

DR LIE: No, nor was there any other neoplastic or endocrine lesion.

DR OLNEY: After reviewing the patient's record in detail would you think Dr Spittell that the possibility of a pheochromocytoma was one that should have been considered by anyone caring for the patient preoperatively?

DR SPITTELL: We all get burned from time to time and I guess I have been burned by just about everything that burns. One of the lessons I have learned is that when I have a patient who has hypertension it is always a good idea to consider the secondary forms of hypertension. If I am going to send a hypertensive patient to surgery I would certainly like to have the results of urinary metanephrines.

DR LIE: Pheochromocytoma is a tumor of neuroectodermal origin that arises from the chromaffin cells of the sympathoadrenal system. Pheochromocytoma is not a common tumor; its estimated frequency among the general population is approximately 1 per 200,000 per year. In the 50 years since Dr Charles H. Mayo reported the first successful surgical resection of a pheochromocytoma from this institution we now have in our autopsy files 54 patients with pheochromocytoma among the 40,078 consecutive autopsies performed in the period 1928 to 1977. This relatively high autopsy incidence of 0.13% would suggest that a significant number of these tumors may be clinically unsuspected. This turned out to be precisely the case when we reviewed the records of these patients. The diagnosis of pheochromocytoma was not made clinically in 41 (76%) of the 54 patients. Among the other 13 patients in whom the existence of a pheochromocytoma was known during life the diagnosis was

sociocultural mobility and changing life events is persuasive data from animal experiments directly and unmistakably links psychosocial disruptions to pathological changes in the cardiovascular system. It is interesting that the prevalence of coronary artery disease and hypertension generally parallels the increasing complexity and ambiguity of social systems and social hierarchies whether we are speaking of animals or mankind. Given the complexity of human interactions and psychology, it is understandable that we should begin this discussion with the more well controlled experiments conducted in the less cognitively complex members of the animal kingdom.

Work summarized by Mason² has shown that psychosocial stimuli can elicit either of two neuroendocrine responses. One response involves arousal of the pituitary-adrenal cortical system and the other that of the sympathetic-adrenal medullary system. Social interactions resulting in downward displacement in the social hierarchy lead to stimulation of the pituitary-adrenal cortical system with mental depression, decreased gonadotropin levels, enhanced vagal activity, gluconeogenesis and pepsin production. In contrast the sympathetic-adrenal medullary system is called into play as agonistic or competitive behavior is invoked in an attempt to maintain status and prevent threatened loss of esteem and/or related objects of attachment.

A variety of behavioral paradigms have been examined with regard to their influence upon the cardiovascular system in a variety of species. Such animal experiments have included classical conditioning, avoidance conditioning, avoidance yoke procedure, pre-avoidance experience and psychosocial stress.

Classical conditioning. In Pavlovian or classical conditioning experiments a relatively neutral stimulus called a conditioned stimulus is immediately followed by another stimulus called the unconditioned stimulus. After repeated pairing of conditioned stimulus followed by unconditioned stimulus the originally neutral stimulus comes to elicit a pronounced physiologic response. Classically the conditioned stimulus has been a light or tone and the eliciting or unconditioned stimulus has been an aversive stimulus such as electrical shock. Yet it has been observed that when monkeys are given relatively long periods of habituation to restraining chairs with gradual shaping of responses and training sequences that minimize

the ambiguity of stimulus cues the baseline heart rate during conditioning sessions can generally be kept near or even below the intrinsic rate. In contrast when experimentally naive monkeys are given short periods of habituation with large numbers of trials or training sequences that do not minimize ambiguity the pretrial baseline heart rate is significantly in excess of the intrinsic value.³ In classical conditioning therefore, novelty appears to be an important element. Melnoshvili and others⁴ presented three Russian keys with a number of stressful behavioral situations over a period of two years. The most prominent behavioral procedure was one in which a light signal followed by a shock was superimposed upon a bar press response for food. During the first four months on the training schedule the investigators observed that blood pressure increased from baseline levels but subsequently a sustained increase in blood pressure began to develop. When the animals developed new behavior the normal diurnal pattern in blood pressure, heart rate and breathing were greater during the day than at night became altered and the authors observed that the apes were out of phase.

Avoidance conditioning. In the avoidance conditioning experiment the animal is trained to avoid stimulation by making a desired response. During signalled avoidance the experimenter is warned that it must make a desired response to avoid being shocked. In signalled avoidance the animal is required to press a lever at a prescribed interval to avoid receiving shock. A variety of animals engaged in avoidance conditioning reveal an increase in arterial pressure associated with an increase in heart rate, cardiac output and variable changes in peripheral resistance. Several investigators⁵ have demonstrated changes in cardiac electrophysiological properties during avoidance conditioning. Alterations have been implicated in diverse cardiac arrhythmias including ventricular fibrillation. Ernst and associates⁶ using avoidance conditioning trained dogs to diminish coronary flow which uncoupled from other cardiovascular variables as training proceeded, demonstrating that coronary circulation can be independently controlled by a stressful behavioral contingency.

Avoidance yoke procedure. In the avoidance yoke procedure the avoidance animal is trained to manipulate a lever to avoid shock. When

Fundamentals of clinical cardiology

Psychosocial and behavioral influences in the pathogenesis of acquired cardiovascular disease

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Curiously the concept that man's circumstances and emotions importantly influenced his circulation were long ago accepted by observant students of mankind. Indeed, few folklore notions have enjoyed as widespread and persistent popularity as those that ascribe sudden death to emotional shock. Throughout history, anecdotes appear about people dying suddenly in the throes of fear, rage, grief, humiliation, or joy. Yet with the ebb and flow of medical progress in the last century, scientific measurement and laboratory observation assumed increasing importance in the evolution of medicine, and such anecdotes held little sway in the scientific community. Now, history repeats itself and age-old observations are being reexamined as a sizable body of evidence accumulates implicating psychosocial conflict, emotions, and behavioral patterns in the pathogenesis of coronary heart disease, sudden death, cardiac arrhythmias, and systemic hypertension. This interest has been heightened in investigations of coronary heart disease by the observation that the traditional risk factors fail to account for half of the cases of clinical coronary heart disease encountered on a worldwide basis.

It is difficult to separate the role of behavior and environment from the accepted risk factors.

Each risk factor is a composite of genetic, environmental, and behavioral components which can all be provoked, enhanced, or sustained by influences which are beyond simple metabolic or pathophysiologic explanations. Thus, in view of our incomplete knowledge of the pathogenesis of coronary heart disease and the likelihood that additional key factors are operating, it is not surprising that preventive measures confined to a few factors have met with limited success to date. The recent acceptance of Rosenman and Friedman's Type A behavior pattern as a statistically validated major risk factor is but one example of medical interest in psychosocial and behavioral influences. In point of fact, the results from most of the reported epidemiologic studies that generally incriminate the high fat intake of upper middle class Western man as the major cause of elevated serum cholesterol could just as well have been utilized to support the concept that rapid industrialization and the resultant socioeconomic stress were the responsible factors. In addition to dietary intake and tobacco usage, the lifestyle and society of Western industrialized man is distinctly different from that of populations manifesting a lower incidence of coronary heart disease. While a complete understanding of how such influences participate in and are interrelated with other factors in the pathogenesis of cardiovascular disease remains the work of future investigation, this work appears warranted on the basis of what is known and suspected.

Psychosocial and behavioral influences in cardiovascular disease in animals

Whereas epidemiologic evidence linking coronary and hypertensive heart disease with prolonged emotional stress, behavioral patterns

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second is the brain stem hypothalamic system which is concerned with sex, hunger, thirst and sleep drives. It is at the level of cognitive integration, however, where species differences become most apparent and this process involves the frontal association cortex and the parietal and temporal cross modal association areas termed the sociocultural brain. Only in man do these structures attain such overwhelming proportions when compared to the rest of the brain.

Nevertheless the strongest evidence for a potential or substantiated influence of psychosocial and behavioral factors in the pathogenesis of cardiovascular disease in man rests with manipulations of the social hierarchy and interactions of designated animal species. Henry and Fly have demonstrated that fixed hypertension and myocardial hypertrophy, progressive arteriosclerosis, myocardial fibrosis and renal failure can be induced in socially deprived mice by subjecting them to social interaction. Moreover Henry and Fly have shown that at least some of these changes were apparently mediated by an increase in the adrenal enzymes tyrosine hydroxylase and phenylethanolamine N-methyltransferase. The increases observed appeared to reflect a situation in which brief sympathetic discharges, elicited by discontinuous emotional stimuli, were transformed into sustained sympathetic arousal. An important observation in addition to the impact of social manipulation is the fact that different genetic strains of mice have different levels of blood pressure and different potentials for synthesizing adrenal catecholamines. They also have different temperaments responding differently in degree to the same social paradigm. Thus the physiologic consequences of psychosocial provocation are largely engrained upon a foundation of cultural and genetic predisposition.

Von Holst in experiments with tree shrews introduced a subordinate animal to another male who was an experienced fighter. After the subjugated animals were separated from the experienced fighters by a wire mesh but were allowed to continue to observe each other the subordinates would fall into comas within 2 to 16 days despite adequate food and drink and would die in uremia due to renal insufficiency. Until the time of death the uremic subordinates manifested continuous piloerection as a manifestation of sustained sympathetic arousal. Lapin and Cherkovich performed similar experiments in which they altered

the social situation of dominant Hamadryas baboons. The male of this particular species adopts its females when they are still infants and develops an intense attachment for them. When the dominant male was separated from his mate and another male was put into the females' cage in full view of the former consort, the displaced male showed intense agitation. After several months hypertension and other evidence of chronic cardiovascular disease developed in the original consort. While some of the studies were aimed at developing experimental neuroses rather than deliberate cardiovascular disease, the authors encountered a significant number of cases of hypertension, coronary insufficiency and acute myocardial infarction.

Ratcliffe²¹ in studies at the Philadelphia Zoo observed that deaths in animals and birds from arteriosclerotic coronary heart disease increased from an incidence of less than 1% in 1943 to more than 10% in 1968. Diet and mean age at death were no different, but he did note that in 1949 the zoo began an attempt to assemble family groups. This contrived social grouping resulted in conflicts, breeding failures and abnormal behavior within the family groups. He eventually concluded that the increase in coronary heart disease resulted from behavioral responses in these social situations. He then did an experimental follow-up studying the psychological response of swine to separations occurring after the primary social bonds of grouped animals had been formed. At the end of a year the separated animals showed a significantly greater incidence and severity of coronary atherosclerosis. Whereas grouped and paired swine responded to human visitors with friendly grunts and squeals, for a handout those swine that had been separated, especially the normally friendly females, failed to respond to visitors and even refused offers of added corn.

Weber and Vander Walt²² produced coronary opathy in New Zealand white rabbits by alternately housing them singly and then crowding them again. In the course of ten months 30 of the animals had expired with ten dying during the first week, ten more during the first month, and the rest at intervals during the succeeding months. In those dying within a few days, severe myocardial necrosis was observed in the subendocardium and myocardium. Those that survived longer developed foci of myocardial fibrosis and

the animal fails to meet the scheduled requirement both the animal and its yoked partner receive shocks. Thus both animals always receive the same number and temporal pattern of shocks but only the avoidance animal has control over whether shock will occur. In such experiments Corley and colleagues¹² observed that five of six yoked monkeys developed physical deterioration and severe bradycardia with ventricular arrest but no significant myocardial necrosis. In contrast, the avoidance monkeys developed electrocardiographic abnormalities and myocardial degenerative lesions. Such unsignalled avoidance can activate the sympathetic autonomic nervous system yielding a direct action of norepinephrine upon beta receptors in the myocardium which results in myocardial necrosis. Richter³ demonstrated the adverse consequences of yoked helplessness when he demonstrated that rats developed fatal vagally mediated bradycardia after being subjected to severe unavoidable water stress. Interestingly Schneider observed that among patients who had a past myocardial infarction those with the greatest tendency to bradycardia in response to startle also had the poorest prognosis. In Corley and associates' experiments¹ the key difference leading to divergent pathologies was that the animals in the avoid condition had control over whether they received shock but the yoked animals did not. Also the occurrence of shock was somewhat predictable in the avoid but unpredictable in the yoked condition.

Preavoidance experience. Animals subjected to repeated sessions of avoidance conditioning eventually had changes in their baseline cardiovascular physiology during the period immediately preceding the session. Such prior experience can influence the organism's behavioral physiological and biochemical responses. Anderson and Tosheff¹³ studied the cardiovascular responses of dogs during daily sessions consisting of a one hour anticipation period followed by an hour of unsignalled shock avoidance. When the animals were placed in a harness for the hour immediately preceding the daily sessions of unsignalled avoidance the animals manifested a progressive decrease in heart rate and cardiac output accompanied by a progressive increase in total peripheral resistance. Studies by Adams and co-workers¹⁴ using cat fight confrontations with glass partitioned separation demonstrated that shortly

before the episodes of fighting began both heart rate and cardiac output decreased while total peripheral resistance increased. These studies suggest that during an orienting reflex total peripheral resistance increases. The orienting reflex response is hemodynamically similar to the diving reflex and has been elicited by electrical stimulation of the brain stem in rats.¹⁵ This reflex pattern has been suggested as one mechanism for sudden death as manifested in the experiments of Corley and associates¹ using monkeys and Richter³ using rats. Such studies have resulted in the concept of learned helplessness. According to the learned helplessness hypothesis animals exposed to a stressor they cannot control may learn that their behavior cannot control the environment. The biochemical explanation for this behavior appears to involve depletion of brain norepinephrine. Glazer and co-workers¹⁶ found that depletion of monoamines by a single injection of tetrabenazine produced a depressed response to escape in rats when the avoidance escape response involved a relatively high degree of motor activity but not when a minimum of motor activity was required. These investigators also observed that by decreasing the stress induced depletion of monoamines by the use of an MAO inhibitor they could protect the animals from the effects of inescapable shock. Thus the MAO inhibitor reduced the learned helplessness produced by unavoidable shocks. Studies of cardiac somatic coupling by Obrist and colleagues¹⁷ have indicated that vagally mediated reflexive bradycardia occurs in sympathetically aroused animals when these animals inhibit their somatic activity. The vagally mediated cardiac component of the baroreceptor reflex is sufficiently strong to override the concomitant sympathetic activation of the heart.¹⁸

Psychosocial stress. The constellation of influences in cardiovascular disease most clearly approximating those seen in man occur during experiments involving manipulation of the social hierarchy of animal colonies. So far we have discussed a variety of experimental methods resulting in diverse neuroendocrine responses which may be elicited singularly sequentially or in concert. These responses are mediated on the effective integrative level through two major pathways. The first is the limbic striatal system which is involved in the social emotional and self-preservation behavior of animal species. The

costeroid levels which were originally high showed progressive decline while epinephrine and norepinephrine levels showed progressive upward trends. This suggests that the rat altered its response to the experience. Early immobilization might be regarded as a threat against which the animal was helpless, had no coping defenses and a perception of loss of control. However, with repetition, although the event was equally noxious, it was perceived as having a predictable outcome. Thus, there are three major indications from experimental data:

1. Animal studies demonstrate that as a result of emotional arousal, purely cognitive processes can lead to neuroendocrine changes of the adrenal medullary and/or adrenocortical systems and that dependent upon the environmental situation and coping mechanisms available, such responses may be elicited singularly, sequentially, or in concert.

2. Different psychosocial and physiological changes develop according to the emotion predominantly concerned. Anger, challenge, and fear are associated with the fight or flight response and sympathetic adrenal medullary activation with the familiar chain of physiological changes.

3. Depression is found in situations fraught with loss of control, such as feelings of helplessness and subordination. In contrast, it involves activation of the pituitary-adrenocortical system and depression of gonadotropins.

The clinical relevance of these observations is supported by Bourne's studies²⁹ of men during combat in Vietnam and by Katz and colleagues' studies³⁰ of women awaiting biopsy reports of a lump in the breast. Both studies showed that feelings of social acceptance and high personal worth, which commonly accompany effective psychiatric defenses, are associated with decreased activity of the pituitary-adrenocortical system. Carroll's³¹ work complemented these studies and demonstrated that primary depression accompanied by lack of self-worth was associated with the reverse response of increased activation of the adrenal cortex.

In addition, there is an increasing amount of experimental evidence linking the central nervous system to lipid metabolism and atherosclerosis. Chronic stimulation of the ventral medial nucleus of the hypothalamus of cholesterol-fed rabbits significantly elevated plasma cholesterol levels³ and exposure to a continuous auditory stimulus of white noise induced enhanced alimentary

hyperlipemia in rats and rabbits.³² An involvement of adrenal gland activity in the lipemic response to auditory stimuli has been noted. The finding that such stimuli induce a marked increase in adrenocortical steroid secretion, as this activity may persist for some weeks after exposure to auditory stimuli. On the other hand, removal of the adrenal glands and the hypothalamus did not abolish the milieu-induced postprandial hyperlipemia of fat-fed rats.³ However, an electrolytic lesion placed in the anterior hypothalamus does prevent the milieu-induced postprandial hyperlipemia otherwise observed in the animals. Hypercholesterolemia can be induced in rats by bilateral injury of the ventral medial nuclei of the fornices and the medial portions of the lateral hypothalamic nuclei, but cannot be ascribed to any change in function of the thyroid, adrenals, testes, or pituitary that might have been induced by the hypothalamic lesion nor can it be ascribed to any induced derangement of pancreatic discharge of insulin.³³

Studies of spontaneous vascular lesions in animals yield important information which is useful in assessing the role of various risk factors in the process of atherosclerosis. Such animal studies provide baseline data for comparison with experimentally induced arterial lesions in that species and also provide a panorama of the types of lesions which may occur in the animal kingdom. They yield insight into the pathogenesis of arterial disease in particular species, provide information regarding the types of lesions occurring throughout the animal kingdom, and permit formulation of hypotheses concerning arterial disease in general.

Stout and Bohorquez³⁴ have reported that focal atherosclerotic plaques are common in birds, being found in 24% of the aortas. The prevalence of aortic atherosclerosis in birds could not be correlated with the type of diet consumed, captivity or in nature. Fatty streaks and fibrous plaques are quite common in many species of mammals and birds. In seals and sea lions, fibrous plaques are plentiful and similar in morphology and distribution to those occurring in humans.³⁵ However, the fibrous plaque in seals contains no stainable lipid, indicating that a mechanism other than lipid insudation is responsible for the proliferation of intimal smooth muscle cells. The demonstration of a striking correlation between the development of the lesions and the locale of hemodynamic flow

compensatory myocardial hypertrophy in the fibers adjacent to the fibrotic areas

The previous discussion provides ample evidence that environmental novelty and/or adversity particularly when sustained is capable of eliciting physiologic responses which when unbalanced may lead to pathologic consequences. In addition psychosocial interactions are powerful and important influences in eliciting such responses. Henry and Ely⁶ have pointed out however that social stimuli do not act directly on the individual. Rather perception of the social environment as mediated by personality role and status variables arouses emotions which induce physiologic responses. An important aspect of such discussions is that in addition to the impact of social manipulation different genetic strains have different levels of blood pressure and different potentials for synthesizing adrenal catecholamines. They also have different temperaments responding differently in degree to the same social paradigm. Thus the physiologic consequences of psychosocial provocation are largely engrafted upon a foundation of cultural and genetic predisposition and are effected principally through cognitive mechanisms.

It is known that stress such as cold, heat, fasting or exercise fails to elicit typical neuroendocrine responses of either the sympathetic adrenal medullary or pituitary adrenocortical systems if emotional arousal is avoided.²² This has been illustrated in early studies of the effects of three day fasting on two of eight monkeys housed in the same room. The deprived monkeys often vocalized in apparent protest when the caretaker handed food pellets to the others. The elevation of 17 hydroxycorticosteroids on the first day of the fast suggested that psychological as well as nutritional factors might be at work since the fasting monkeys were exposed to all the sights, sounds and stimuli associated with routine feedings and the presence of the nonfasting monkeys. If novelty and uncertainty were carefully minimized by allowing the monkeys time to adapt to experimental conditions outside stimuli eliminated by soundproofing and discomfort minimized by giving the monkeys non nourishing fruit flavored pellets no change in steroid levels occurred during fasting periods. These sorts of studies strongly suggest that rather than social stimuli acting directly on an individual personal assessment of the social environment uniquely

refracted through one's self image and value perceptions arouses emotions which produce physiologic responses.

Within the society whether animal or man a hierarchy exists and approved behavior must be exercised. It is not only man who responds to a life situation by how it affects him personally, a monkey whose parents are dominant members of a troop is likely to attempt a dominant role. Socially deprived and formerly isolated animals that give vent to their irritation at the expense of an infant or a more dominant group member receive short shrift from the infant's parents or an offended social superior. A well adapted subordinate of any species knows he must wait his turn patiently and show respect for those higher in social rank. If a psychosocial stimulus is inhibited at higher levels by interaction with coping patterns it will be perceived as irrelevant within the frame of reference. If perceived as relevant however arousal is triggered and limbic system components respond initiating further trains of responses.

Studying dominant and subordinate males in mouse colonies Ely and Henry²³ verified that change of status is associated with altered neuroendocrine patterns. They demonstrated that the enzyme tyrosine hydroxylase which is under sympathetic control and the rate limiting enzyme in the synthesis of norepinephrine rose more markedly in dominant mice than in subordinates as struggle for status in the newly formed social hierarchy progressed. Phenylethanolamine N methyltransferase which converts norepinephrine to epinephrine not only increased in dominant animals but continued to rise while falling in subordinates as they adapted to a loss of status. Once the mice adapted to each other in the colonies these changes were no longer seen during later stages of interaction as the social hierarchy stabilized. On the other hand during the unstable phase of the social hierarchy subordinates demonstrated marked increases in plasma cortisol levels which returned to normal levels when the social hierarchy became stable and established. Whereas challenge and anxiety elicit sympathetic and adrenal medullary responses loss of control and depression are associated predominantly with corticosteroid responses. Studies indicate that a gradual shift occurs in the nature of a rat's response to immobilization when taped to a laboratory bench. With repeated experience corti-

per capita consumption of alcohol. Some of the recognized factors contributing to the psychological distress in this society were (1) the perceived national urgency of putting a man on the moon by the end of 1969, (2) the great national and international visibility of the Center in which a dramatic failure would have adverse occupational consequences, (3) the problems of interpreting and coordinating the work of approximately 300 different major industrial contractors particularly for administrators and managerial personnel engaged in interorganization liaison, (4) the progressive decline in budget and employment and (5) the resultant threat of loss of employment identity and income from lack of demand for overspecialized and highly trained skills inappropriate to the common marketplace. In short, the project demanded an ever increasing if not frenzied pace of production with the ultimate reward of nearly inevitable dismissal, financial loss and loss of professional identity.

There were findings of an unusually high percent of abnormal resting electrocardiograms.²⁰ In addition there was a remarkable incidence of psychoneuroticism, anxiety and depression within the population.²¹ Postmortem myocardial histologic features of victims of sudden death demonstrated the existence of hyperfunctional anomalous contraction bands. This same histologic picture of hyperfunctional necrosis can be quickly induced in the hearts of animals by the administration of boluses of catecholamines.²² The abilities of catecholamines to facilitate rhythm disturbances increase myocardial oxygen demand, augment vascular reactivity and mobilize free fatty acids, are well established facts. The results of animal experimentation have demonstrated the protective effect of pretreatment with beta blockade, and recent studies suggest that beta blocker therapy has a beneficial impact upon the incidence of coronary death in some countries. Many years ago Raab maintained that corticosteroid administration potentiated and augmented the myocardial degenerative influences of catecholamine administration in animals. Animal experimentation strongly suggests that the combination of heightened sympathetic arousal followed by a complete sense of hopelessness and helplessness is a particularly lethal combination for the development of sudden death.²³ In a national sense the KSC workers were struggling winners, who finally did achieve in

putting a man on the moon. In a personal and professional sense the inevitable dismissal and loss of professional and financial security resulted whether they succeeded or failed at their mission. This placed many of them in a situation of being ultimate losers in a joyless struggle. For most highly specialized aerospace personnel the Kennedy Space Center experience was an overall Pyrrhic victory on a personal level. The combined factors of arousal, struggle, loss and helplessness are clearly evident in retrospect in this study and are hauntingly reminiscent of a multitude of experiments employing yoked and restrained animals.

A large number of experimental animal studies have strongly implicated psychological stress as the precipitator of arrhythmias and sudden death. Several reports have recently appeared in the literature documenting the effects of psychological stress in lowering the threshold for ventricular fibrillation and sudden death both in animals and in man.²⁴⁻²⁷ The combination of arousal with enforced helplessness and extreme conflicting stimulation has been demonstrated by Gelhorn² to result in breakdown of the reciprocity between the fight or flight reaction and the playing dead reaction. Under overhelming stress both systems become active simultaneously or in rapid alternation with each other. This constitutes the neurophysiologic basis for the behavioral disorganization typically exhibited by animals under extreme stress: the dog that starbles, crouches, trembles, moves about aimlessly, barks, whines, salivates, urinates, defecates, pants, piloerects and sometimes momentarily dozes. All these activities indicate simultaneous or rapidly alternating sympathetic-parasympathetic activation.

Although it is difficult to conduct controlled human studies comparable to those readily obtained in animals, electrocardiographic monitoring during a variety of psychologically stressful tasks in humans has documented sinusoidal and potentially fatal rhythm disturbances in direct association with episodes of emotional stress.²⁸ Thus it appears that continuous ECG monitoring can provide previously unavailable physiologic data on the process of dying. Advanced technology is beginning to illuminate pathologic physiologic processes which may offer guidance to the factors which can lead to lethal consequences and techniques suitable for their control. □

suggests that mechanical stress may be an important operative factor. Stout and colleagues²⁷ have also demonstrated that chronic low intensity electric shock is associated with an increased proliferation of aortic fibrous plaques in minipigs. While many investigators feel that entrapment plaque necrosis in human atherosclerosis is due to accumulation of lipids within the cells of the plaque, atherosclerotic plaques of giant anteaters and aardvarks manifest central plaque necrosis before lipid accumulation.²⁸ Moreover, recurrent areas of focal plaque necrosis apparently involving smooth muscles were found within fibrous plaques in a number of species. These areas of focal necrosis were also present within fibrous plaques of experimental pigs receiving chronic electric shock.

It is apparent from the foregoing discussion that atherosclerosis presents manifold countervailing forces but is relatively commonplace in the animal kingdom. However, captive birds seem to show a higher incidence of atherosclerosis, perhaps because of their higher blood pressures and serum cholesterol levels.

Regarding the influence of serum lipids in the atherosclerotic process, it has been shown that there is a bidirectional transfer of cholesterol between the normal aorta with equal movement of lipid in and out of the endothelium. However, when the intima becomes abnormal, lipid movement into the arterial wall predominates. Superimposed upon this ubiquitous atherosclerotic lesion are species-specific factors. It seems that attributes of a species are a preponderant factor in the development of atherosclerosis. It is certain that being a bird is more important than the type of diet consumed, since granivorous birds have far more atherosclerosis than do granivorous animals and so on. A unique peculiarity of human atherosclerosis is the sequelae of thrombus formation and thus implies that platelet aggregation plays a significant role in the ischemic sequelae. It is against this background of animal and experimental information that the role of psychosocial factors and behavior in the pathogenesis of contemporary clinical cardiovascular disease will be viewed and discussed.

Clinical cardiovascular disease

We may look at cardiovascular disease in terms of distinct entities such as hypertension, coronary heart disease and sudden death, but we must recognize that they seldom stand in isolation and

that overlapping relationships exist. The clinical observations linking psychosocial, environmental and behavioral factors with atherosclerotic and hypertensive cardiovascular disease, arrhythmogenesis and sudden death are too extensive to permit a comprehensive discussion within the scope of this review and the reader is referred to a number of reviews in the literature.²⁹ We will briefly highlight some observations regarding psychosocial and behavioral factors as they relate to sudden death, coronary heart disease and hypertension. These will then be synthesized into a composite of hypothetical mechanisms that may interrelate the accepted risk factors.

Sudden death

Few folklore notions have enjoyed as wide spread and persistent popularity as those that ascribe sudden death to emotional shock. Far back in recorded history, people are described as dying during emotional upheaval. Almost 2000 years ago, Celsus³⁰ described that emotional states could influence the heart. William Harvey³¹ reaffirmed the observation in 1628 by stating that fear and every affection of the mind that is attended by either pain or pleasure, hope or fear is the cause of an agitation whose influence extends to the heart. In more recent times, such influences have been causally implied by Hunter's³² prediction of the circumstances of his death and by Cannon's³³ observations on 'voodoo death'. Even Osler³⁴ commented on the behavioral aspects of sudden coronary death in his straightforward and simple description of the coronary-prone individual as a 'keen and ambitious man, the indicator of whose engines is set at full speed ahead'. However, with the advent of scientific medicine in the late nineteenth century, such observations fell into disrepute as scientific and traditional medical approaches dictated that the cause of death should be established at the necropsy table and in the laboratory.

As an epidemiologic phenomenon, the incidence of sudden death at the Kennedy Space Center during the mid 1960s strongly suggested the influence of psychosocial and behavioral factors. Although traditional risk factors were not remarkable, the sudden death rate among men at the Kennedy Space Center (KSC) was nearly 50% higher than that of age and sex matched control groups (Warheit and Eliot, unpublished manuscript). The divorce rate was three out of four marriages and this microcosm led the nation in

members of the cohort. The diets of all the chimpanzees contained 10% of total calories as fat. Both animals manifesting predominant coronary and cerebral atherosclerosis had adjusted poorly to captivity showing neurotic traits such as stereotyped posturing, hoarding of food and other objects and poor socialization with peer animals in the colony.

While dietary fat intake appears to be statistically important, the documented observations that dietary cholesterol is limited in absorption and that most cholesterol is manufactured in the liver suggests that other factors might be importantly involved. It is curious that Friedman and colleagues' studies⁴¹ of accountants demonstrated that their highest serum cholesterol levels consistently occurred during periods of severe occupational and emotional stress. Conversely, minimal values occurred during periods of minimal stress despite unchanged levels of dietary fat intake. While fat feeding rabbits to produce atherosclerosis has been carried out as a reliable animal model for the last 60 years, Neren⁴² reports that if the animals are fondled or given daily doses of diazepam, the extent of atherosclerosis is significantly reduced despite comparable levels of attained hypercholesterolemia. Thus, the association between dietary intake of fat and atherosclerosis is an incomplete association. One should recognize that the dietary hypothesis arose primarily from studies involving prosperous industrialized competitive societies and restrained fat fed socially isolated animal models.

A third risk factor is cigarette smoking, and there is little question that carbon monoxide inhalation and nicotine exposure have definite physiologic consequences. Nicotine is a stimulator of both sympathetic and parasympathetic ganglia and increases the arterial epinephrine concentrations in man. Nicotine also induces ADH secretion, liberates catecholamines from the heart, increases heart rate and cardiac output, lowers the threshold for ventricular fibrillation and causes peripheral vessel constriction. Nicotine increases free fatty acids in serum through its catecholamine release and usually promotes the development of atherosclerotic lesions in fat fed animals.⁴³ Necrosis and calcification of the medial layers of aorta were often seen in these animals and this might be explained by an effect of catecholamines since their administration to animals has a similar effect. The effect if any of smoking on blood coagulation and the function of

platelets is probably related to an action of nicotine since carbon monoxide exposure does seem to have any effect. Carbon monoxide does induce arterial hypoxia which accelerates atherosclerosis in cholesterol fed rabbits.⁴⁴ There is no qualitative difference between lesions in animals exposed to carbon monoxide and animals exposed to hypoxia.

However, in addition to powerful physiologic effects, it is obvious that smoking constitutes a cultural and behavioral phenomenon as well. Keys' seven country study⁴⁵ the findings were that nonsmokers consistently differed from smokers in being relatively heavier and fatter and tended to have higher blood pressures, except in Japan where there was no consistent difference. Light smokers tended to have lower serum cholesterol values than their fellows in the same sample but otherwise serum cholesterol showed little or no relationship to smoking habits in most areas. Exceptions were in Slovenia, Montenegro, Crete and Corfu where nonsmokers tended to have higher cholesterol values and in Vukov Kraina, Yugoslavia where the opposite tendency prevailed. In general, the higher blood pressures in the nonsmokers could not be explained by the excess of obese men in this group. Indeed, the high prevalence of smoking in Corfu and Japan correlated negatively with electrocardiographic findings of coronary heart disease, a statistical anomaly at variance with studies of United States populations.

There are obvious health reasons for discouraging the smoking habit, yet it appears obvious that genetic and sociocultural behaviors might participate in modifying results in the etiologic relationship between cigarette smoking and atherosclerotic coronary heart disease. In addition to its identity as a risk factor, cigarette smoking is a sociocultural behavior which in some societies and cultures is negatively or insignificantly correlated with atherosclerosis. These comments are not intended to minimize the health consequences of the smoking habit but merely to point out that despite the powerful physiologic effects of tobacco smoke, there is not an immutable relationship with coronary heart disease in all populations, cultures and societies. In studying this risk factor's relationship to coronary atherosclerosis, the sociocultural and motivational aspects of the habit should be examined in addition to its prevalence.

An additional link to be considered in the

Perhaps equal importance is the fact that animal studies have taught us that the same experimental environments may produce different results in different species dependent upon genetic, experimental and cognitive functions. Different results may also be obtained by altering time frames or options within animals of the same species. Such findings indicate that the impact and countervailing of a psychosocial stimulus in the human as in various animal species, is related to individual cognitive functions, circumstantial novelty and psychological defenses. The likelihood of an event eliciting an adverse physiologic response depends also upon a complex amalgam of factors including genetic predisposition, early social experience and a lifelong process of conditioning and cultural factors.

Therefore, we believe that ambulatory monitoring as a measure of physiologic response should be correlated with aspects of cognitive behavior. The influence of psychosocial and behavioral factors is becoming increasingly well substantiated in the clinical areas of arrhythmogenesis and sudden death. A variety of physiologic mechanisms contributing to these clinical phenomena are being discovered and examined. The aspects of cognitive integration eliciting such responses remain an important frontier for further investigation.

Atherosclerotic coronary heart disease

While the link between observed environmental provocation and physiologic response is relatively immediate and direct in studies of sudden death, the role of psychosocial and behavioral factors in coronary heart disease is far more complex and elusive yet these appear to be culpable. Considering the slow evolution of clinical coronary heart disease and our incomplete knowledge of the pathophysiology of atherosclerosis and the mechanisms of its sequelae, one can hardly expect more proof than guilt by association. Because we really do not fully understand the mechanism whereby any heretofore commonly accepted coronary risk factor effects arterial damage, we still have to determine the intrinsic pathophysiological metabolic and neurochemical processes which over prolonged periods of time intervene in the onset of clinical coronary heart disease. When such fundamental mechanisms are understood it should not be too difficult to track down the precise cardiopathic pathways which

might be fostered by psychosocial and behavioral factors.

At the present state of our understanding it appears that the atherosclerotic process involves injury and proliferation of intimal smooth cells with subsequent alteration in permeability and/or metabolism and tends to occur at bifurcating or originating sites of vessel branches. With the progressive insudation of lipid material, hemodynamic impairment to flow eventually results. The site of lesion formation suggests that hydrodynamic stress and shear forces participate in the process. This also suggests that the higher and more frequent kinetic energy trauma to the circulation at these points of turbulence the more rapid the evolution of the lesion. While these findings are consistent with hypertension as a risk factor it is obvious that additional factors are operative. Those individuals possessing the C3⁺ gene in essential hypertension have a coronary risk rate nearly seven times higher than those who are C3⁻ negative. Furthermore, epidemiologic studies in Japan suggest that in some populations the incidence of hypertension may be remarkably high without a concomitant increase in atherosclerotic findings. Thus the association is incomplete but it is generally accepted that elevated blood pressure and increased shearing forces constitute an aggravating cause in the development of atherosclerosis. The behavioral aspects of hypertension will be discussed later.

A second factor having obvious face validity is that enhanced lipid availability is an integral part of the atherosclerotic process. Here also psychosocial and behavioral factors appear to be involved. Dietary fat intake has long been incriminated as the major factor in this process, notably through some epidemiologic studies and by fat feeding various animal species. Nevertheless, several observations suggest that dietary fat intake is not exclusively related to the process. Andrus and associates¹ published one attempt to induce atherosclerosis in chimpanzees through high fat high cholesterol feeding. In that study it was interesting that although there were more aortic fatty streaks in the experimental animals than in controls, this difference was less pronounced in the epicardial coronary arteries and there was no difference in the cerebral arteries. Stout and Bohorquez² found epicardial and cerebral atherosclerosis in two of their chimpanzees which was significantly advanced over that found in other

2 Serum lipids whether available through dietary substrate or mobilized by central nervous system factors enhance and foster smooth muscle cell proliferation and become incorporated within the proliferative and necrotic lesion.

3 The smoking habit through its nicotine effects on catecholamine excretion and consequent physiologic effects in collaboration with the effects of carbon monoxide upon vascular permeability tends to promote mechanisms contributing to atherogenesis.

4 Platelet mobilization and aggregation directed toward areas of endothelial trauma release a platelet derived growth factor and the vasoconstrictive agent thromboxane A_2 contributing to smooth cell proliferation in combination with vasoconstrictive constriction.

Many of the incriminated mechanisms appear to work through or are activated by catecholamines in concert with hyperlipemia. Catecholamines are probably the most important factors promoting lipid mobilization. They are effective in mobilizing lipid from adipose tissue both by their liberation from non adrenergic nerve terminals in adipose tissue and by their secretion from the adrenal medulla into the blood. The free fatty acids not stored or utilized in the production of energy are eventually taken up by the adipose tissues or by the liver. Free fatty acids taken up by the liver are formed into triglycerides and are secreted as components of very low density lipoproteins. The rate at which the liver secretes very low density lipoproteins is determined partly by the rate it synthesizes free fatty acids from carbohydrates and partly by the rate it receives free fatty acids in the blood. In the fasting state the secretion of very low density lipoproteins by the liver is determined principally by the levels of free fatty acids in the blood. These levels in turn are determined principally by the effects of catecholamines on adipose tissue and by the rates of energy production. Catecholamines promote platelet adhesiveness and aggregation promote arrhythmias and lower the threshold to arrhythmia generation and increase secretion of glucagon, thyroxine, calcitonin, parathormone, renin, erythropoietin and histamine while diminishing insulin secretion. Glucocorticoids convert protein into carbohydrate and fat have a minor antagonistic effect on insulin promote the development of diabetes, foster hyperlipidemia and hypercholesterolemia enhance water diuresis

diminish circulating lymphocytes reduce $Le-L_2$ cytolysis and polycythemia increase platelet counts with an enhancement of clotting tendencies lower the electrical excitation threshold of the brain increase gastric acidity and peristalsis production block growth hormone secretion decrease calcium absorption enhance arginine vasopressin production sensitize arterioles to the pressor effect of catecholamines and decrease the inflammatory response. Accelerated atherosclerosis is one of the main causes of death in Cushing's syndrome whereas the sequelae of pheochromocytoma include hypertensive crises myocardial infarction with or without coronary disease arrhythmias and catecholamine myocarditis. Both of these endocrine excesses have been demonstrated to occur in reactions to various psychosocial circumstances mediated by cognitive perceptions.

Type A behavior

The term Type A behavior was coined by Friedman and Rosenman¹⁴ almost two decades ago, but the association between a typical behavioral pattern and victims of coronary heart disease had been previously recognized by others including Oler's succinct description¹⁵ at the turn of the century. A recent conference sponsored by the National Heart Lung and Blood Institute appraised the role of behavior as a predictor of potential coronary heart disease.¹⁶ The review panel convened by this Institute accepted the available body of scientific evidence as demonstrating that Type A behavior as defined by the structured interview used in the Western Collaborative Group Study, the Jenkins Activity Survey and the Framingham Type A behavioral scale was associated with an increased risk of clinically apparent coronary heart disease in middle aged US citizens. The risk was found to be beyond that imposed by age, elevated systolic blood pressure, serum cholesterol, or cigarette smoking and appeared to be of at least the same order of magnitude as the relative risks associated with the latter three of these factors.

Type A behavior was described as an aroused state superimposed on a complex underlying substrate of interrelated factors.¹⁷ Metaphorically it can be viewed as an iceberg with a small portion apparent above the surface. Unfortunately, situational or environmental determinants, individual perceptible or cognitive differences and other per-

atherosclerotic chain of events is the role of platelets and thrombosis. This phenomenon appears to be distinctive for atherogenic sequelae in man as compared to the rest of the animal kingdom. If smooth muscle cell proliferation, lipid accumulation and thrombosis are parts of the atherosclerotic mosaic, clotting and platelet function must be suspected as potentially culpable agents in the process. It has been suggested that repeated or chronic endothelial cell loss may be the principal event leading to atherosclerosis.⁶⁶ Furthermore, the intimal lesions that occur in homocysteinemia induced or mechanically induced arteriosclerosis can be prevented by pharmacologic agents that interrupt platelet consumption or by inducing a thrombocytopenia with an anti serum of platelets.⁶⁷ The endothelium normally regulates the entrance of low density lipoproteins (LDL), the principal cholesterol carrying lipoprotein of the plasma, into the artery wall. Low density lipoproteins also support smooth muscle proliferation in cell culture. Although LDLs may be mitogenic, they more probably provide nutrients necessary for cell proliferation in terms of new membrane formation. Human fibroblasts contain specific receptor sites for LDL and arterial smooth muscle cells are thought to have similar receptors that play a role in controlling the intracellular synthesis of cholesterol. Recent investigations demonstrate that platelet alpha granules contain platelet derived growth factor (PDGF), a potent stimulator of smooth muscle cell proliferation.⁶⁸ Since increased platelet activity in vitro has been reported in patients with familial hypercholesterolemia, it is necessary to determine whether the decreased survival is a direct effect of increased cholesterol or lipoproteins upon the platelets or is a manifestation of increased platelet consumption by exposed subendothelial surfaces.

Ross and Harker⁶⁹ performed matched cross over platelet survival experiments in normal, lipidemic and hyperlipidemic monkeys and demonstrated that platelets from hyperlipidemic monkeys survived normally after infusion into normal lipidemic animals. In contrast, platelets from normal lipidemic animals infused into hyperlipidemic animals had a decreased survival time comparable with that of autologous platelets. While such data do not rule out the possibility of a rapidly occurring lipid mediated effect on the membranes of transfused platelets, the reduction in platelet survival is most consistent with

increased platelet consumption on exposed subendothelial surfaces as observed in the desquamation associated with homocysteinemia and in prostheses such as artificial valves or vessels. Platelet derived growth factor (PDGF) in contrast to the situation with other polypeptide hormones is distinctive in that the predominant delivery system for PDGF is the platelet rather than the plasma. PDGF is primarily carried through the circulation in the alpha granules of the platelet and while it is in this cryptic state it cannot stimulate cell replication. Since platelets have an affinity for injured sites, they provide a remarkably specific delivery system for this polypeptide hormone which initiates the replication of arterial smooth muscle cells in vitro and may do so in vivo.

As a further support of the role of platelets in atherosclerosis, it should be remembered that pigs with von Willebrand's disease have a defect in platelet adhesion. Bowie and associates⁷⁰ showed that such animals failed to develop the atherosclerotic lesions that occur in control animals made hypercholesterolemic by a fatty diet. Thus a suspected fundamental response following some form of injury to the endothelium may be platelet mediated intimal smooth muscle proliferation. In addition, when vascular damage leads to platelet deposition in the endothelial wall, liberation of the vasoconstrictor thromboxane A₂ occurs, tending to propagate the platelet aggregation process and perhaps collaborating in the development of coronary spasm.⁷¹ Enzymatic formation of prostacycline is specifically inhibited in vitro by lipid peroxide such as 15 hydroperoxyarachidonic acid and inhibition of the formation of this thrombolytic agent by lipid peroxides may provide an explanation for the development of some thrombotic episodes. A variety of studies have demonstrated the ability of catecholamines to enhance platelet stickiness and aggregation while other studies have demonstrated increased platelet aggregation and consumption under a variety of situations, both emotional and physical, broadly referred to as stress.⁷²

To summarize what is known and highly suspected about the hypothesized roles of the various risk factors in the atherogenic process:

1. Hypertension increases local vascular trauma, turbulence, with its greatest hydrodynamic impact at branching sites of vascular origin and serves as an instrument for inducing mechanical trauma.

might be called competitive arousal struggle for dominance and the expected psychomotor consequences of the fight or flight mechanism. With regard to the previously mentioned animal studies concerning alterations in the environment it seems reasonable to suspect that environmental stress and sociocultural factors importantly influence the type of behavior observed. Industrialized western societies have in common a depersonalized complexity and reward system for the effective competitor. In general these societies tend to reward those who are time urgent and aggressive. Thus in some ways there is a curious resemblance between Henry and Ely's studies of an agonistic society in mice and contemporary industrialized societies.

We would contend that a social structure which positively reinforces competition aggression and time urgent performance would result in a perpetual dynamic struggle for status and dominance so characteristic of the Type A psychomotor behavioral pattern. Such behavior reinforced and rewarded by agonistic societies is attended by all the previously discussed physiologic mechanisms implicated in the pathogenesis of coronary atherosclerosis. These include large fluctuations in blood pressure, excessive catecholamine and ACTH production, enhanced lipid mobilization and increased platelet aggregation.

Such observations do not deny the importance of innate physiologic reactivity nor should we minimize the important influence of heredity. Nevertheless if we are to talk about risk factors as phenomena which may accelerate or foster the biologic time clock of a degenerative process, the psychosocial and behavioral factors discussed provide a unifying link between epidemiologic and pathophysiologic mechanisms in the study of coronary atherosclerosis. We still must elucidate the intrinsic processes whereby such factors lead to the onset of clinical coronary heart disease. Yet when such fundamental mechanisms are understood it should not be too difficult to understand the role of emotion and the neuroendocrine system in fostering such processes.

Hypertension

Hypertension affects approximately 35 million Americans and can be traced to an identifiable cause in less than 10% of the cases. Despite the widespread popular conception that an inner feeling of nervous tension is in fact hypertension, we know that objective evidence for such equiva-

lency is nonexistent. However, a sizeable and diverse number of scientific observations strongly suggest that psychosocial and behavioral factors participate in the pathogenesis of hypertension. The ability of adverse psychosocial situations to evoke chronic hypertension was alluded to earlier in the work of Henry. While the strength of evidence in the clinical arena is less than that for objective controlled animal experiments, such psychosocial factors as socioeconomic level, crime rate, residential change and overcrowding have been linked with hypertension.

Harburg and colleagues¹ have shown that blacks living in areas of Detroit with low ecological stress had less hypertension than their counterparts living in high stress areas. Gampel and co-workers² have reported that there was less hypertension among rural than among urban Zulus; of the latter more of those who cling to traditional cultural practices and seemed unable to successfully adapt to the demands of urban living were hypertensive. In general a remarkable contrast can be found between industrialized and primitive societies that demonstrates the relative absence of hypertension in the latter. Yet immigrants from primitive societies to urban communities develop hypertension with equal or greater incidence facility and severity. Apropos to these observations is the comment of Ostfeld and Sherkelle³: "There has been an appreciable increase in uncertainty of human relations as man has gone from the relatively primitive and more rural to the urban and industrial. Contemporary man in much of the world is faced every day with people and with situations about which there is uncertainty of outcome wherein appropriate behavior is not prescribed and validated by tradition where the possibility of bodily or psychological harm exists where running or fighting is inappropriate and where mental vigilance is called for."

In reality the agonistic society of Henry and Ely's animal experiments is tantamount to the society of urbanized industrialized man. However just as different genetic strains of the same species manifest different temperaments and potential for developing hypertension, it is likely that similar modifiers are operative in the clinical setting. Whatever provocation or stress may emanate from a social environment, genetic predisposition and cognitive integration are equally important factors in the equation resulting in hypertension. The mosaic theory of pathophysi-

chological components such as anxiety depression psychosocial problems and physiological variations pathophysiological aging mechanisms and genetic susceptibility are not easily assessed. Clearly the most diagnostic of the available tests in the assessment of Type A behavior is the structured interview of Friedman and Rosenman. None however was considered satisfactory with regard to prognostic sensitivity specificity and selectivity in predicting the advent of coronary heart disease. The panel did however recommend that the structured interview be considered the most suitable as a standard at this time. The Type A behavior as evaluated by the structured interview is manifested by behavioral styles of loud explosive rapid and accelerated speech with short response latency hostility and a tendency toward verbal competition.

Speed impatience hostility competitive drive and a sense of an effort oriented person caught up in a joyless struggle constitute the fully developed Type A behavior pattern. Glass observations that the Type A personality is vulnerable to depression are in accord with the results of a study by Thomas Ross and Duszynski of physicians with myocardial infarcts who readily became depressed even as students and likewise with the results of a study by Bruhn and colleagues of the coronary prone individual as an effort oriented person whose achievements give him little satisfaction.

The mechanisms through which Type A behavior operates as a risk factor and by which it facilitates the progression of coronary heart disease remain conjectural. A weakness shared with all risk factors until the pathogenesis of coronary atherosclerosis is fully understood. However the prevalence of certain biochemical and physiological phenomena are highly associated with fully developed Type A behavior. These include elevated serum cholesterol levels elevated pre and postprandial serum triglycerides enhanced platelet aggregation faster clotting time higher excretion of norepinephrine particularly when provoked by emotional challenge a higher average serum level of corticotropin a greater insulinemic response to glucose a decreased growth hormone response to arginine and greater lability and magnitude of blood pressure response under time demand tasks.

It is important to make a distinction between Type A behavior and the ill defined but constant

ly evolving concept of coronary prone behavior. Individuals manifesting Type A behavior may survive uncathed into old age attending the funerals of their younger Type B counterparts. Thus the association is incomplete. It is obvious that genetic perceptive and other coping factors operate to counterbalance predisposing behavioral effects in many individuals and only certain components of Type A behavior correlate with coronary heart disease. Furthermore the cognitive integrative aspects of behavior and their link to pathophysiologic responses remain largely unknown.

If by behavior one means the actions or reactions of man or animals under specified circumstances a recent study by Dembroski and associates illustrates the distinction between behavior in coronary patients and in non coronary control patients. During a structured interview and an American history quiz they noted an increase in systolic blood pressure during the history quiz in Type B coronary patients but not in Type B controls. Indeed the greatest increment of blood pressure change in either Type A or B groups was evoked in Type II myocardial infarction patients during the American history quiz. Such observations suggest that we must attempt to examine and integrate the multifaceted aspects of overt psychomotor behavior with those of cognition and physiologic behavior if we are to gain further understanding of how behavioral facets translate into coronary proneness.

Yet if we return to what is known and suspected concerning the pathophysiology of the other risk factors it is obvious that each represents a single manifestation of a more complex underlying process. What constitutes the fundamental pathophysiology remains conjectural but it is relatively certain that the orchestration of such factors occurs in a living emotional reacting organism attempting to adapt to its environment in the interest of maintaining its own integrity. A variety of psychosocial and conditioning experiments in animals point clearly to mechanisms attending the development of accelerated atherosclerosis and the neuroendocrine system as undoubtedly of pivotal importance in orchestrating the pathophysiologic mechanisms culminating in atherosclerosis.

Type A behavior is recognized by its psychomotor components which in the fully developed pattern are easily recognized as signs of what

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ogy proposed by Page²⁴ seems appropriate and useful. From this vantage point the socioenvironmental association with hypertension seen in a variety of epidemiologic studies suggests that social or emotional stress may play a role in the pathogenesis of hypertension. Controversies concerning the term environmental stress aside we find it more understandable and therefore more useful to view stress by its effect upon the organism in question, that effect being strain. Therefore we know stress by the company it keeps namely strain. It seems necessary for perceptive and cognitive processes to determine whether outside forces represent for that individual a strain inducing phenomenon. There is no other apparent explanation for the old adage that beauty is in the eye of the beholder.

Beyond considerations of environmental provocation psychological and behavioral aspects are also worthy of note. Work by Alexander²⁵ suggests that the hypertensive personality may be described as an individual who frequently manifests inhibited and poorly expressed rage and anger. It has been proposed that this inhibited rage or anger turned inward results in stimulation of the autonomic nervous system which causes the release of significant amounts of norepinephrine leading to acute and eventually chronic hypertension. The influence of catecholamines upon renin release has already been mentioned and Esler and colleagues have reported that in psychometric testing patients with high renin hypertension exhibited suppressed hostility linked to increased sympathetic activity. In these patients the hypertension was concluded to be neurogenic and possibly psychosomatic in origin. Such individuals are described as withdrawn not easily communicative and tending to avoid confrontation with people even when rage is justified. At times such individuals may seem obsequious in their efforts to avoid conflict in order to please those individuals with whom they are involved in interpersonal relationships.

On the other hand it may be somewhat naive to postulate that personality patterns influence the autonomic nervous system and thus produce hypertension. Others have suggested that this behavior may be a manifestation of an awareness by hypertensives of their hyperreactive cardiovascular system and the observed behavior represents attempts to withdraw from confrontation lest they evoke excessive and potentially harmful responses.²⁶ Work by some investigators sug-

gests that hypertensive patients deny the difference between a neutral and an overtly confrontational movie drama as if in some manner they had managed to avoid perceiving what was an obvious confrontation.²⁷

Studies have indicated that 25% to 40% of patients with essential hypertension are characterized by higher basal circulating catecholamine levels and by higher sympathetic activity in response to postural changes.²⁸ The identification of these patients as a separate entity is desirable since it is possible that the evolution of the hypertensive disease and response to therapy may differ in this group.

Whether observations linking personality behavior and neuroendocrine mechanisms with hypertension constitute valid clues to the pathogenesis of essential hypertension or a protective response to genetic vulnerability or even a functional defect as a consequence of the disease process remains to be elucidated. However a wide variety of experimental and clinical observations implicate psychosocial and behavioral factors in the phenomenon of essential hypertension. The interaction between mind and environment engrafted upon a genetic substrate is a complex topic for study. Yet the foregoing discussions of neuroendocrine mechanisms and consideration of the concept that essential hypertension represents specific disturbances or shifts in the bias of physiologic regulatory mechanisms is consistent with observed data in epidemiologic experimental and clinical data. Since either adrenal medullary or adrenal cortical systems can lead to hypertension and are known to be activated by psychosocial stimuli with concomitant behavioral phenomena it is not too difficult to see that repeated exposure to such stimuli can lead to structural vascular thickening and mechanically increased resistance. Whereas initially the imbalance is probably reversible chronically repeated and sustained arousals are likely to result in a permanent dysregulatory state with fixed hypertension. One cannot underestimate the importance of psychosocial and neuroendocrine elements early but it is likely that these become less significant in the later stages of hypertension.

Summary

When taken together studies relating psychosocial and behavioral factors to cardiovascular disease phenomena provide justification for the conclusion that such factors are importantly

might be called competitive arousal struggle for dominance and the expected psychomotor consequences of the fight or flight mechanism. With regard to the previously mentioned animal studies concerning alterations in the environment it seems reasonable to suspect that environmental stress and sociocultural factors importantly influence the type of behavior observed. Industrialized western societies have in common a depersonalized complexity and reward system for the effective competitor. In general these societies tend to reward those who are time urgent and aggressive. Thus in some ways there is a curious resemblance between Henry and Ely's studies⁹ of an agonistic society in mice and contemporary industrialized societies.

We would contend that a social structure which positively reinforces competition aggression and time urgent performance would result in a perpetual dynamic struggle for status and dominance so characteristic of the Type A psychomotor behavioral pattern. Such behavior reinforced and rewarded by agonistic societies is attended by all the previously discussed physiologic mechanisms implicated in the pathogenesis of coronary atherosclerosis. These include large fluctuations in blood pressure, excessive catecholamine and ACTH production, enhanced lipid mobilization and increased platelet aggregation.

Such observations do not deny the importance of innate physiologic reactivity nor should we minimize the important influence of heredity. Nevertheless if we are to talk about risk factors as phenomena which may accelerate or foster the biologic time clock of a degenerative process, the psychosocial and behavioral factors discussed provide a unifying link between epidemiologic and pathophysiologic mechanisms in the study of coronary atherosclerosis. We still must elucidate the intrinsic processes whereby such factors lead to the onset of clinical coronary heart disease. Yet when such fundamental mechanisms are understood it should not be too difficult to understand the role of emotion and the neuroendocrine system in fostering such processes.

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lency is nonexistent. However, a sizeable and diverse number of scientific observations strongly suggest that psychosocial and behavioral factors participate in the pathogenesis of hypertension.² The ability of adverse psychosocial situations to evoke chronic hypertension was alluded to earlier in the work of Henry. While the strength of evidence in the clinical arena is less than that for objective controlled animal experiments, and psychosocial factors as socioeconomic level, emigrate residential change and overcrowding have been linked with hypertension.

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In reality the agonistic society of Henry and Ely's animal experiments is tantamount to the society of urbanized industrialized man. However just as different genetic strains of the same species manifest different temperaments and potential for developing hypertension it is likely that similar modifiers are operative in the clinical setting. Whatever provocation or stress may emanate from a social environment genetic predisposition and cognitive integration are equally important factors in the equation resulting in hypertension. The mosaic theory of pathophysiol-

Appraisal and reappraisal of cardiac therapy

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Antihypertensive therapy New pharmacological approaches

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Over the last 30 years an increasing proportion of hypertensive subjects have come to be treated with antihypertensive drugs. The first drugs used, though life saving in their day, were too toxic and were replaced by others which produced fewer side effects. Knowledge of the sites and mechanisms of action of antihypertensive agents has greatly increased. Newer agents have been developed for greater selectivity. However, there has not been a corresponding growth in the understanding of the pathogenesis of hypertension, nor is it yet feasible in the clinic to analyze the mechanisms giving rise to hypertension in individual patients. Indeed, it has been claimed that the concept of prospectively individualizing antihypertensive therapy remains largely hypothetical. These considerations may help to explain why, despite a steady flow of interesting new antihypertensive substances from the pharmaceutical industry, clinical trials have often failed to confirm that greater specificity in drug action achieves a better therapeutic result. We appear to have reached a plateau in therapeutic efficacy. It may then be asked: does a precise knowledge of the specific sites and mechanisms of drug action really help in choosing treatment for the individual patient with high blood pressure? Further, what justification exists for prescribing the more selective drugs?

We propose that understanding the action of an antihypertensive agent helps to predict and

recognize its side effects, to avoid adverse interactions with other drugs, and to obtain additive hypotensive effects by combining it with drugs acting elsewhere. Such information is integral to the design of systems of stepped care therapy, through which individualization of treatment, though empirical, can proceed along rational lines. In this review, we will outline what is known about the modes of action, the side effects, and the applications of currently available antihypertensive drugs, and will analyze their contributions to a system of stepped care therapy.

1 Mechanisms of action and interaction of antihypertensive drugs

Antihypertensive drugs fall into four main groups: diuretics, angiotensin inhibitors, vascular smooth muscle relaxants, and sympatholytic drugs. The clinical relevance of the angiotensin inhibitors is yet to be clearly defined, and they are restricted to investigational use at present.

1 Diuretics These act principally by causing renal loss of sodium and water, with reduction in intravascular volume and cardiac output. In the early stage of diuretic therapy, the hypotensive effect reflects mainly a fall in cardiac output.¹ In the later stage, secondary adjustments restore cardiac output, but blood pressure control is maintained through peripheral vasodilatation. Discussion of the differences between the diuretics in their renal tubular actions is beyond the scope of this paper, but may be found in the review by Seely and Dirks.²

2 Angiotensin inhibitors act by preventing the effects of the renin-angiotensin system upon vascular smooth muscle, and possibly upon the adrenal cortex, kidney, and brainstem. Angioten-

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might be called *competitive arousal struggle* for dominance and the expected psychomotor consequences of the fight or flight mechanism. With regard to the previously mentioned animal studies concerning alterations in the environment it seems reasonable to suspect that environmental stress and sociocultural factors importantly influence the type of behavior observed. Industrialized western societies have in common a depersonalized complexity and reward system for the effective competitor. In general these societies tend to reward those who are time urgent and aggressive. Thus in some ways there is a curious resemblance between Henry and Ely's studies⁹ of an agonistic society in mice and contemporary industrialized societies.

We would contend that a social structure which positively reinforces competition aggression and time urgent performance would result in a perpetual dynamic struggle for status and dominance so characteristic of the Type A psychomotor behavioral pattern. Such behavior reinforced and rewarded by agonistic societies is attended by all the previously discussed physiologic mechanisms implicated in the pathogenesis of coronary atherosclerosis. These include large fluctuations in blood pressure, excessive catecholamine and ACTH production, enhanced lipid mobilization, and increased platelet aggregation.

Such observations do not deny the importance of innate physiologic reactivity nor should we minimize the important influence of heredity. Nevertheless, if we are to talk about risk factors as phenomena which may accelerate or foster the biologic time clock of a degenerative process, the psychosocial and behavioral factors discussed provide a unifying link between epidemiologic and pathophysiologic mechanisms in the study of coronary atherosclerosis. We still must elucidate the intrinsic processes whereby such factors lead to the onset of clinical coronary heart disease. Yet when such fundamental mechanisms are understood it should not be too difficult to understand the role of emotion and the neuroendocrine system in fostering such processes.

Hypertension

Hypertension affects approximately 35 million Americans and can be traced to an identifiable cause in less than 10% of the cases. Despite the widespread popular conception that an inner feeling of nervous tension is in fact hypertension, we know that objective evidence for such equiva-

lency is nonexistent. However, a sizeable and diverse number of scientific observations strongly suggest that psychosocial and behavioral factors participate in the pathogenesis of hypertension. The ability of adverse psychosocial situations to evoke chronic hypertension was alluded to earlier in the work of Henry. While the strength of evidence in the clinical arena is less than that for objective controlled animal experiments, such psychosocial factors as socioeconomic level, erratic residential change, and overcrowding have been linked with hypertension.

Harburg and colleagues¹⁰ have shown that blacks living in areas of Detroit with low ecological stress had less hypertension than their counter parts living in high stress areas. Gampel and co-workers¹¹ have reported that there was less hypertension among rural than among urban Zulus, of the latter more of those who clung to traditional cultural practices and seemed unable to successfully adapt to the demands of urban living were hypertensive. In general a remarkable contrast can be found between industrialized and primitive societies that demonstrates the relative absence of hypertension in the latter. Yet immigrants from primitive societies to urban communities develop hypertension with equal or greater incidence, facility and severity. Appropos to these observations is the comment of Ostfeld and Shakelle¹²: "There has been an appreciable increase in uncertainty of human relations as man has gone from the relatively primitive and more rural to the urban and industrial. Contemporary man in much of the world is faced every day with people and with situations about which there is uncertainty of outcome wherein appropriate behavior is not prescribed and validated by tradition where the possibility of bodily or psychological harm exists where running or fighting is inappropriate and where mental vigilance is called for."

In reality the agonistic society of Henry and Ely's animal experiments¹⁰ is tantamount to the society of urbanized industrialized man. However, just as different genetic strains of the same species manifest different temperaments and potential for developing hypertension it is likely that similar modifiers are operative in the clinical setting. Whatever provocation or stress may emanate from a social environment, genetic predisposition and cognitive integration are equally important factors in the equation resulting in hypertension. The mosaic theory of pathogenesis

ogy proposed by Page⁴⁴ seems appropriate and useful. From this vantage point the socioenvironmental association with hypertension seen in a variety of epidemiologic studies suggests that social or emotional stress may play a role in the pathogenesis of hypertension. Controversies concerning the term environmental stress aside we find it more understandable and therefore more useful to view stress by its effect upon the organism in question, that effect being strain. Therefore we know stress by the company it keeps, namely strain. It seems necessary for perceptive and cognitive processes to determine whether outside forces represent for that individual a strain inducing phenomenon. There is no other apparent explanation for the old adage that beauty is in the eye of the beholder.

Beyond considerations of environmental provocation, psychological and behavioral aspects are also worthy of note. Work by Alexander⁴⁵ suggests that the hypertensive personality may be described as an individual who frequently manifests inhibited and poorly expressed rage and anger. It has been proposed that this inhibited rage or anger turned inward results in stimulation of the autonomic nervous system which causes the release of significant amounts of norepinephrine leading to acute and eventually chronic hypertension. The influence of catecholamines upon renin release has already been mentioned, and Esler and colleagues⁴⁶ have reported that in psychometric testing patients with high renin hypertension exhibited suppressed hostility linked to increased sympathetic activity. In these patients the hypertension was concluded to be neurogenic and possibly psychosomatic in origin. Such individuals are described as withdrawn, not easily communicative and tending to avoid confrontation with people even when rage is justified. At times such individuals may seem obsequious in their efforts to avoid conflict in order to please those individuals with whom they are involved in interpersonal relationships.

On the other hand, it may be somewhat naive to postulate that personality patterns influence the autonomic nervous system and thus produce hypertension. Others have suggested that this behavior may be a manifestation of an awareness by hypertensives of their hyperreactive cardiovascular system and the observed behavior represents attempts to withdraw from confrontation as they evoke excessive and potentially harmful responses.⁴⁷ Work by some investigators sug-

gests that hypertensive patients deny the difference between a neutral and an overtly confrontational movie drama as if in some manner they had managed to avoid perceiving what was an obvious confrontation.⁴⁸

Studies have indicated that 25% to 40% of patients with essential hypertension are characterized by higher basal circulating catecholamine levels and by higher sympathetic activity in response to postural changes.⁴⁹ The identification of these patients as a separate entity is desirable since it is possible that the evolution of the hypertensive disease and response to therapy may differ in this group.

Whether observations linking personality, behavior and neuroendocrine mechanisms with hypertension constitute valid clues to the pathogenesis of essential hypertension or a protective response to genetic vulnerability or even a functional defect as a consequence of the disease process remains to be elucidated. However, a wide variety of experimental and clinical observations implicate psychosocial and behavioral factors in the phenomenon of essential hypertension. The interaction between mind and environment engrafted upon a genetic substrate is a complex topic for study. Yet the foregoing discussions of neuroendocrine mechanisms and consideration of the concept that essential hypertension represents specific disturbances or shifts in the bias of physiologic regulatory mechanisms is consistent with observed data in epidemiologic, experimental and clinical data. Since either adrenal medullary or adrenal cortical systems can lead to hypertension and are known to be activated by psychosocial stimuli with concomitant behavioral phenomena, it is not too difficult to see that repeated exposure to such stimuli can lead to structural vascular thickening and mechanically increased resistance. Whereas initially the imbalance is probably reversible, chronically repeated and sustained arousals are likely to result in a permanent dysregulatory state with fixed hypertension. One cannot underestimate the importance of psychosocial and neuroendocrine elements early but it is likely that these become less significant in the later stages of hypertension.

Summary

When taken together, studies relating psychosocial and behavioral factors to cardiovascular disease phenomena provide justification for the conclusion that such factors are importantly

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Table 1 Main classes and generic names of antihypertensive drugs in general use

| A Diuretics | | | |
|------------------------------------|----------------------------------|---|-----------------------|
| (a) Thiazide and related diuretics | (b) Loop diuretics | (c) Osmotic | (d) Potassium-sparing |
| Chlorothiazide | Furosemide | Ticrynafene | Spironolactone |
| Cyclopentiazide | Ethacrynic acid | | Tamoxifen |
| Bendroflumazide | Bumetanide | | Amiloride |
| Methyclothiazide | | | |
| Metolazone | | | |
| B Angiotensin inhibitors | | | |
| (1) Angiotensin antagonists | (b) Converting enzyme inhibitors | | |
| | | | |
| C Vascular smooth muscle relaxants | | | |
| Hydralazine | Diazoxide | Nifedipine | |
| Minoxidil | Verapamil | Sodium nitroprusside | |
| D Sympatholytic drugs | | | |
| (a) Centrally acting | (b) Internally acting | (c) β adrenergic blockers (site of action unclear) | |
| Reserpine | { | Propranolol | |
| Methyldopa | | Oxprenolol | |
| Clonidine | | Alprenolol | |
| Guanabenz | | Pindolol | |
| Tiamenidine | { | Sotalol | |
| Guanfacine | | Timolol | |
| | | Acebutolol | |
| | { | Metoprolol | |
| | | Atenolol | |

Ganglion blocking drug excluded

†Neuron blocking drugs

‡Alpha adrenergic receptor blocking drugs

§Combined alpha and beta adrenergic receptor blocking drug

angiotensin II on its receptors whereas converting enzyme inhibitors interfere with the conversion of angiotensin I to angiotensin II. Unfortunately controversy surrounds the mode of action of the potentially most useful member of this group the converting enzyme inhibitor captopril. This drug the only angiotensin inhibitor yet developed which is effective by the oral route, also potentiates the kinin system and possibly produces its hypotensive action in part through this or other still undefined pharmacologic mechanisms. Nevertheless a recent review of 19 hypertensive patients treated for periods of up to 6 months has shown that the blood pressure reduction produced by captopril is correlated both with the pretreatment plasma renin activity and with the suppression of urinary aldosterone excretion.

3 Vascular smooth muscle relaxant drugs alter cellular calcium flux and cause direct vasodilatation.¹⁰ Their actions are independent of alpha and beta adrenoreceptors.

4 Sympatholytic drugs interfere with neuro-

humoral transmission at various points in the sympathetic nervous system. Thus the latter group can be divided on a pharmacological basis into many classes. However from a therapeutic viewpoint the simple classification shown in Table I will suffice.

The ways in which the centrally acting drugs lower blood pressure are still unclear but they have in common the ability to reduce central sympathetic outflow. This may be demonstrated most graphically by showing the decreased rate of spontaneous firing of pre-ganglionic sympathetic neurons after administration of the drug into the cerebral ventricular system.¹¹ In the case of methyldopa, clonidine and guanfacine like drugs (guanabenz, tiamenidine and guanfacine) the reduction of sympathetic traffic appears to result from an alpha adrenergic agonist effect operating on the central inhibitory pathways leading to the vasomotor center, although other central mechanisms of action have been proposed for clonidine.¹² Reserpine causes depletion of catecholamines from both central and sympathetic neurons.¹³ The action of methyldopa is thought to

Appraisal and reappraisal of cardiac therapy

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Antihypertensive therapy New pharmacological approaches

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Over the last 30 years an increasing proportion of hypertensive subjects have come to be treated with antihypertensive drugs. The first drugs used though life-saving in their day were too toxic and were replaced by others which produced fewer side effects. Knowledge of the sites and mechanisms of action of antihypertensive agents has greatly increased. Newer agents have been developed for greater selectivity. However there has not been a corresponding growth in the understanding of the pathogenesis of hypertension nor is it yet feasible in the clinic to analyze the mechanisms giving rise to hypertension in individual patients. Indeed it has been claimed that the concept of prospectively individualizing antihypertensive therapy remains largely hypothetical. These considerations may help to explain why despite a steady flow of interesting new antihypertensive substances from the pharmaceutical industry clinical trials have often failed to confirm that greater specificity in drug action achieves a better therapeutic result. We appear to have reached a plateau in therapeutic efficacy. It may then be asked does a precise knowledge of the specific sites and mechanisms of drug action really help in choosing treatment for the individual patient with high blood pressure? Further what justification exists for prescribing the more selective drugs?

We propose that understanding the action of an antihypertensive agent helps to predict and

recognize its side effects to avoid adverse interactions with other drugs and to obtain additive hypotensive effects by combining it with drugs acting elsewhere. Such information is integral to the design of systems of stepped care therapy through which individualization of treatment though empirical can proceed along rational lines. In this review we will outline what is known about the modes of action, the side effects and the applications of currently available antihypertensive drugs and will analyze their contributions to a system of stepped care therapy.

1 Mechanisms of action and interaction of antihypertensive drugs

Antihypertensive drugs fall into four main groups: diuretics, angiotensin inhibitors, vascular smooth muscle relaxants, and sympatholytic drugs. The clinical relevance of the angiotensin inhibitors is yet to be clearly defined and they are restricted to investigational use at present.

1 Diuretics These act principally by causing renal loss of sodium and water with reduction in intravascular volume and cardiac output. In the early stage of diuretic therapy the hypotensive effect reflects mainly a fall in cardiac output.¹ In the later stage secondary adjustments restore cardiac output but blood pressure control is maintained through peripheral vasodilatation. Discussion of the differences between the diuretics in their renal tubular actions is beyond the scope of this paper but may be found in the review by Seely and Dirks.²

2 Angiotensin inhibitors act by preventing the effects of the renin-angiotensin system upon vascular smooth muscle and possibly upon the adrenal cortex, kidney and brainstem. Angioten-

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Table II Homeostatic reflexes opposing blood pressure control

- 1 Baroreceptor reflexes
 - (a) Alpha adrenoceptor mediated vasoconstriction
 - (b) Beta adrenoceptor mediated cardiac stimulation
- 2 Renal retention of salt and water
- 3 Renin-angiotensin system

been proposed.¹⁴ However, agents recently developed for beta 1 receptor blocking selectivity (metoprolol, atenolol) have proved to be at least as effective in reducing blood pressure as the non-selective beta 1 and beta 2 receptor antagonists. Thus it has been possible to decrease some of the undesired effects of beta 2 receptor blockade without loss of antihypertensive efficacy.

Proper application of drugs of the sympathetic group may be of critical importance in the treatment of severe hypertension because they counteract the baroreceptor-mediated homeostatic reflexes which combat the antihypertensive effect of the other groups of drugs (see Table II). While there are several types of drugs acting at different sites which can interrupt sympathetic neural traffic to the vascular alpha-adrenoreceptors, the only antihypertensive agents which block the cardiac limb of the baroreceptor reflex are the beta-adrenergic blockers. It should be noted that they serve this important function in addition to exerting a hypotensive effect of their own. Agents which diminish reflex cardioacceleration in less specific ways include clonidine (by central vagotonic and peripheral pre-synaptic alpha-receptor agonist interactions) and indoramin (by direct negative chronotropic effect).

A second homeostatic function that may interfere with blood pressure control is the renal retention of salt and water which occurs whenever kidney perfusion pressure drops. This mechanism operates, tending to restore the blood pressure to a high level, when potent smooth muscle relaxant or sympatholytic drugs are used without adequate diuretic therapy. The term *false tolerance* has been coined to emphasize the subtle nature of this problem which can exist in the absence of demonstrable edema. To overcome such tolerance it may be necessary to use large doses of loop diuretics, especially in patients with renal impairment.

Another renal mechanism which can override the effects of antihypertensive agents is activa-

tion of the renin-angiotensin system. Increased circulating levels of renin and angiotensin, together with an increased hypotensive response to angiotensin inhibitors, are found during treatment with diuretics or smooth muscle relaxant drugs. Conversely, maintenance therapy with beta-blockers reduces plasma renin activity to an extent determined mainly by the intrinsic sympathomimetic activity of the particular beta-blocker used,¹⁵ and the influence of concomitant therapy. In general, the centrally acting sympatholytic drugs also decrease renin release, whereas the peripherally acting class have a variable effect.

To summarize, the primary action of hypotensive drugs can be opposed by homeostatic reflexes listed in Table II. Failure to respond to therapy may reflect the influence of one or more of these. It is often possible to recognize the particular mechanism operative in an individual patient. For example, during treatment with a potent vasodilator agent, the occurrence of weight gain or an increase in measured blood volume would point to the need for additional diuretic therapy, whereas the presence of tachycardia and a high cardiac output state might call for the addition of a beta-blocker to the therapeutic regimen.

II Side effects: Relevance to the application of particular drugs

A thorough knowledge of the side effects encountered with various antihypertensive drugs is essential for choosing the most suitable agent for each individual patient. Side effects which can be anticipated and which may influence the choice are discussed below.

A Diuretics

1 *Hypotolemia* A fall in blood volume may occur immediately after the introduction of a diuretic therapy or with the intermittent use of a diuretic. Because of the associated hazard of hypotension and blood hyperviscosity, a risk of precipitating cerebral ischemia exists in patients with cerebrovascular disease. Thus the potent diuretics such as furosemide should rarely be used in elderly subjects and diuretic therapy avoided altogether in patients with transient ischemic attacks.

2 *Hyperuricemia* Most diuretics tend to increase serum uric acid concentration, probably because of an increased passive reabsorption of urate.

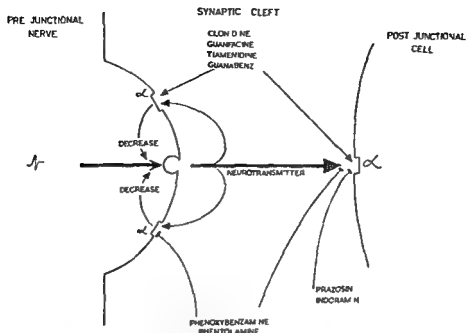


Fig 1 Actions of some antihypertensive agents on the alpha-adrenergic receptors of the peripheral neuro-effector junction. \rightarrow = agonist effect \rightarrow receptor blockade

depend on its active metabolites, including alpha-methylnorepinephrine, which has a potent alpha-agonist effect centrally but little peripheral effect. Clonidine and its congeners have been shown to exert a potent agonist effect at the pre-synaptic alpha receptors of the sympathetic neuroeffector junction (see Fig 1). This property, which causes a diminished release of neurotransmitter, may contribute to the decrease in circulating catecholamines observed in patients treated with clonidine¹³ or guanfacine.¹ These agents also have a relatively weak peripheral post-junctional alpha-agonist effect, which may result in an initial pressor response following their intravenous administration.¹

Those antihypertensive drugs which are known to have a predominantly peripheral site of action include the adrenergic neuron blocking agents and the alpha-adrenergic receptor blockers (Table I). The ganglion blockers, which interfere with parasympathetic as well as sympathetic pathways, are now of historical interest only and have no part in the present-day treatment of hypertensive cardiovascular disease (although they still have a limited role in blood pressure control during anesthesia and in the treatment of aortic dissection, e.g. trimethaphan). The adrenergic neuron blockers are taken up into the nerve ending by uptake, the mechanism responsible

for re-uptake of neurotransmitter norepinephrine. They displace the neurotransmitter in storage granules and also interfere directly with the coupling of nerve impulses to exocytotic release. Alpha-adrenergic receptor blockers lower blood pressure by preventing the agonist effect of neurotransmitter upon the post-junctional alpha receptors at the sympathetic myoneural junctions of vascular smooth muscle (Fig 1). They may be classed as relatively selective (e.g. prazosin) or non-selective (e.g. phenoxylbenzamine), depending upon the degree to which the pre-junctional alpha receptors are also blocked. It has been suggested that pre-junctional alpha-adrenergic blockade, which interferes with the negative feedback control of neurotransmitter release, is disadvantageous and may account for the greater problems encountered with phenoxylbenzamine in clinical practice than with prazosin.¹⁴ Labetalol, a new antihypertensive agent with both alpha and beta-adrenergic receptor blocking actions, is more potent at beta receptors than at alpha receptors in man, but it is not known which of these effects is of the greater importance in reducing blood pressure during chronic oral administration.¹

It has not been established how beta-adrenergic receptor blocking drugs lower blood pressure. Various central and peripheral sites of action have

severe fluid retention " " Pericardial effusion may occur without generalized edema " Hypertrichosis occurs in both sexes and the growth of facial hair commonly causes distress in women However calcium thioglycolate depilatory cream is effective in removing unwanted facial hair and causes little or no skin irritation thus allowing continuation of minoxidil therapy in women with hypertension resistant to other agents "

DIAZOXIDE Diazoxide has had its widest use in hypertension as an injectable solution given intravenously in a dose of 150 to 300 mg for the control of hypertensive crises A rapid fall in blood pressure tachycardia transient hyperglycemia and stimulation of renin release occur after injection " The latter effect has proved useful in diagnosing renovascular hypertension " Because it causes reflex tachycardia and increases cardiac output diazoxide should not be used to treat the severe hypertension associated with aortic dissection " The chronic administration of diazoxide by mouth although effective in controlling severe hypertension associated with renal failure is diabetogenic in about two thirds of subjects and may induce extrapyramidal symptoms "

VERAPAMIL Verapamil has received much more attention as an antianginal and antiarrhythmic compound than as an antihypertensive agent However its potent smooth muscle relaxant effect produces a fall in blood pressure " when the drug is administered orally or intravenously Constipation due to the relaxation of visceral smooth muscle is common " Since verapamil impairs atrioventricular conduction and myocardial contractility it should not be given to patients with heart block or cardiac failure nor should it be used in combination with beta adrenergic blocking drugs "

NIFEDIPINE This new vasodilator which was originally proposed for use in coronary vascular disease has a potent hypotensive action which lasts for 3 to 8 hours after oral or sublingual administration of a 20 mg dose " Side effects reported with its use include sensations of heat in the face and limbs and ankle edema Compared to verapamil nifedipine has a much less pronounced effect on the heart and may be used in combination with a beta blocking agent

SODIUM NITROPRUSSIDE Infusion of nitroprusside is an alternative to the use of diazoxide infusion in hypertensive crises Constant monitoring of blood pressure and plasma thiocyanate

concentration is required to maintain blood pressure control and to prevent toxic encephalopathy " These objectives can be facilitated by the use of a microprocessor to control the rate of infusion "

D Sympatholytic drugs

a Centrally acting sympatholytic agents

1 SIDE EFFECTS RELATED TO CENTRAL INHIBITORY ACTIVITY AND INTERACTIONS WITH ANTICHOLINERGIC THERAPY All centrally acting antihypertensive drugs may cause significant drowsiness and sedation which often improves spontaneously as therapy continues Those in widespread clinical use (reserpine methyldopa and clonidine) have each been associated with an appreciable incidence of severe depression Tricyclic antidepressant drugs may interfere with the antihypertensive actions of clonidine " or methyldopa " probably due to interactions at the central alpha adrenoreceptors in the brainstem Unfavorable interactions may also occur between monoamine oxidase inhibitors and methyldopa In view of the problems which can arise during the management of depressive patients receiving centrally acting antihypertensive agents they should not be prescribed for patients with a previous history of endogenous depression except in the exigency of known resistance to peripherally acting antihypertensive agents

2 WITHDRAWAL REACTIONS In patients treated with clonidine for severe hypertension abrupt withdrawal of this agent can provoke a syndrome characterized by acute hypertension tachycardia and other features of sympathetic discharge " " Similar reactions have been reported after acute withdrawal of methyldopa " guanabenz " and guanfacine " Considerable doubt exists however concerning the incidence magnitude and clinical importance of true overshoot hypertension during withdrawal reactions There have been numerous case reports of severe and occasionally disastrous hypertensive crises after stopping clonidine and three groups have reported features of sympathetic overactivity with or without overshoot hypertension " " " after controlled withdrawal of the drug " " Conversely others have found no evidence of sympathetic overactivity after withdrawal of the drug apart from raised urinary norepinephrine excretion " All these studies have been criticized on various grounds including lack of pretreatment blood pressure data and insufficiently close monitoring during the withdrawal phase The observa-

the kidney accompanying compensatory shifts of proximal tubular fluid. In the case of ticrynafen this tendency is countered by specific inhibition of the reabsorption of both filtered and secreted urate.¹ Clinical gout is precipitated in only a small proportion of patients who develop hyperuricemia as a result of treatment with a diuretic. In such individuals or in those who present with a history of gout of hyperuricemia a number of therapeutic strategies are available: a Avoid the use of diuretics completely. b Use ticrynafen. c Use a diuretic plus probenecid (which inhibits renal tubular reabsorption of urate). d Use a diuretic plus allopurinol which inhibits the production of uric acid. If there is evidence of increased uric acid turnover, options (a) and (d) are preferable to (b) and (c), both of which promote uricosuria and can cause crystalluria.^{1a}

3 *Changes in serum potassium levels.* All diuretics except those of the potassium conserving class (Table I) increase distal tubular potassium secretion and can lead to an appreciable fall in serum potassium concentration. This may have serious consequences in patients receiving digitalis or in those with primary aldosteronism, liver disease or pre-existing potassium depletion. However, diuretic-induced hypokalemia rarely produces problems in patients with uncomplicated hypertension. Potassium conserving diuretics tend to produce hyperkalemia when given to patients with diabetes mellitus²⁸ or impaired renal function. Means of potassium supplementation and their relative efficacy and safety have been reviewed recently.²⁹

4 *Carbohydrate intolerance.* Thiazide diuretics may cause a rise in blood sugar in diabetic patients¹ and may occasionally induce hyperglycemia and glycosuria in previously normal people.¹ Carbohydrate intolerance has also been reported with the use of loop diuretics.³ The mechanism is not wholly understood³⁰ but there is evidence for both impaired pancreatic insulin release and defective glucose utilization by peripheral tissues. Thus a relative contraindication to diuretic therapy exists in patients with diabetes mellitus or known carbohydrate intolerance. This however should not countermand the use of diuretics in such subjects when their hypertension is resistant to other therapy or is complicated by fluid retention.

5 *Hypercalcemia.* Chronic administration of

thiazide and related diuretics reduces calcium excretion by a mechanism analogous to that which pertains to urate.¹ A rise in serum calcium may result. This is usually minor but could be deleterious in patients with pre-existing hypercalcemia due to metabolic disorders such as hyperparathyroidism.

6 *Angiotensin inhibitors.* Administration of the oral converting enzyme inhibitor captopril has induced febrile reactions,³¹ rashes,³² loss of taste sensation³³ and reversible renal failure.³⁴ Intravenous administration of the angiotensin analog saralasin acetate has been associated with pheochromocytoma crisis occurring during the infusion and rebound hypertension with encephalopathy occurring one to three hours after stopping the infusion.³⁵ In general angiotensin inhibitors may produce severe depressor responses in conditions of strong angiotensin II dependency such as extreme sodium depletion, renovascular hypertension and intercurrent therapy with diuretic or vasodilator drugs.³⁶

C Vascular smooth muscle relaxants

1 *Side effects common to all smooth muscle relaxant drugs.* The symptoms of a hyperkinetic circulatory state (flushing, headache and pounding in the ears or chest) may be observed with any drug which produces vasodilatation by a direct action on arteriolar smooth muscle. Tachycardia and fluid retention resulting from unopposed homeostatic adjustments (already outlined) are also common to all drugs of this group. All these symptoms may be countered by the adjunctive use of sympatholytic or diuretic agents, this being essential with the more potent drugs of the group such as minoxidil.

2 Side effects peculiar to particular smooth muscle relaxant drugs

HYDRALAZINE. The most important side effect of hydralazine is the development of a syndrome resembling systemic lupus erythematosus. The drug is best avoided in patients with a family history of lupus and dosage should be restricted to a ceiling of 200 mg per day in known slow acetylators or in subjects with renal impairment. Other side effects specific to hydralazine have been reviewed by Alarcon Segovia and associates.

MINOXIDIL. This drug, the most potent of the orally active peripheral vasodilators, is potentially life saving for refractory hypertension coupled with progressive renal impairment but may cause

Table III Some contraindications to the use of certain drugs in hypertension

| Condition | Drugs contraindicated |
|------------------------------------|---|
| Gout | Thiazide diuretics |
| Hyperurcemia | Loop diuretics |
| Hypokalemia | |
| Hypercalcaemia | Thiazide diuretics |
| Depression | Reserpine methyl dopa Clonidine |
| Poor drug compliance | Clonidine |
| Transient ischemic attacks | Potent diuretics |
| Old age | Adrenergic neuron blockers Alpha adrenergic blockers |
| Treatment with toxic substances | Adrenergic neuron blockers Clonidine methyl dopa |
| Angina pectoris | Smooth muscle relaxants |
| Tachycardia | Alpha adrenergic blockers |
| Cardiac failure | Beta adrenergic blockers Verapamil |
| Bradycardia | |
| AV block | |
| Asthma | Beta adrenergic blockers |
| Insomnia | |
| Raynaud's syndrome | Non selective beta blockers |
| Calf Claudication | |

Except in the presence of beta adrenergic blockade

lower in incidence with beta 1 selective blockers than with those of indiscriminate beta 1 and beta 2 affinity. However increased selectivity has resulted in limited gains because receptor selectivity is relative and not absolute and also because most organs appear to have populations of both beta 1 and beta 2 receptors despite a dominance of one type or the other. Presumably the cardioselective drugs should have less tendency to produce bronchospasm or exacerbate symptoms of peripheral vascular disease. However severe asthmatic reactions and Raynaud's phenomenon have been reported with the use of these selective agents. All beta blockers should be avoided in asthmatic patients or in subjects who give a history of persistent wheeze during respiratory infections and similarly in patients with peripheral gangrene or other evidence of severe vasospasm. Beta blockers are not contraindicated in hypertensive diabetic subjects except perhaps those whose control is brittle or those prone to frequent hypoglycemic reactions. Beta 1 selective blockers are preferable for use in diabetic patients.²⁰ The question of whether beta 1 selectivity improves diastolic blood pressure control

Table IV Some indications for the use of certain drugs in hypertension

| Condition | Drugs used |
|------------------------------|---|
| Cardiac failure | Diuretics (all) |
| Edema | |
| Hyperurcemia | Thiazides |
| Hypokalemia | Non-converting diuretics |
| Migraine | Clonidine Beta adrenergic blockers |
| Angina | Beta adrenergic blockers Verapamil |
| Palpitations | |
| Ectopic beats | |
| Arrhythmias (not all) | Beta adrenergic blockers |
| Recent myocardial infarction | Beta adrenergic blockers |
| Essential tremor | Propranolol |
| Severe cardiac failure | Furosemide Hydralazine Sodium nitroprusside Nifedipine |

during stress is unresolved. Although exogenous epinephrine produces less rise in diastolic pressure during beta 1 blockade than during non selective beta blockade this phenomenon does not necessarily hold for situations of endogenous catecholamine release from the adrenal medulla or sympathetic nerve terminals.²¹

III A system of stepped-care therapy

The questions to be considered in selecting drug treatment for a given patient with hypertension are

1 What characteristics of the patient constitute indications or contraindications for the use of particular drugs?

2 Having decided which drugs suit the patient what options exist for their use in appropriate combinations if combined therapy proves necessary to control the hypertension?

The first of these decisions involves patient drug matching while the second involves the matching of drug to drug in combinations which achieve additive hypotensive effects but minimize side effects. Contraindications to specific drugs and classes of drugs have been discussed and some of the more important examples listed in Table III. Certain indications for particular drugs are given in Table IV.

These considerations form a background to

difficulties in carrying out and interpreting appropriate experiments in hypertensive patients has pointed to the need for controlled studies in normotensive subjects and in experimental animals. We have demonstrated significant overshoots in blood pressure and heart rate 16 to 24 hours after even single doses of clonidine or guanfacine in normotensive rats.^{7, 68} Another group has confirmed these findings although they failed to demonstrate overshoot in hypertensive rats.⁶

It is the authors' opinion that the hazards of clonidine withdrawal are real enough to warrant avoiding this drug in patients who have a history of poor compliance with drug therapy. If chronic oral medication with clonidine is interrupted by acute gastrointestinal disorders or the need for general anesthesia, therapy may be continued by the intramuscular route.⁷

3 OTHER RELEVANT SIDE EFFECTS OF CENTRALLY ACTING ANTIHYPERTENSIVE AGENTS

Drugs in this class may occasionally cause sexual dysfunction in males and so threaten compliance. Since bowel disturbances may result from treatment with methyldopa or clonidine, it is preferable to avoid using these agents in patients with enterocolitis. Reserpine especially when given in large doses may aggravate peptic ulcer disease. Postural hypotension occurs infrequently with both methyldopa and clonidine but is more prominent with guanabenz which has a subsidiary peripheral adrenergic neuron blocking effect.⁷

b Peripherally acting sympatholytic agents

1 SIDE EFFECTS OF NEURON BLOCKING DRUGS

The side effects of this class which is long established in clinical therapy are well known and will not be detailed here. The most important are postural hypotension, diarrhea and interruption of the ejaculation reflex. The antihypertensive action of neuron blockers is severely impaired by tricyclic antidepressant therapy,⁷² probably through competition for the neuronal uptake process.

2 SIDE EFFECTS OF ALPHA ADRENERGIC RECEPTOR BLOCKING DRUGS. Postural hypotension has been the most frequent and troublesome side effect with alpha adrenoceptor antagonists. Hence it is inadvisable to use these drugs in the elderly or in subjects with known cerebrovascular or coronary insufficiency. Particularly severe reactions have been reported after the initial dose of prazosin or as a response to dosage increments

of this agent. This first dose phenomenon is aggravated by prior sodium depletion⁷ or by the presence of renal failure.⁴ It has been attributed to selective blockade of visceral sympathetic activity⁷³ but usually subsides despite continued therapy. The problem is minimized by starting with a small dose in the evening.¹⁶ However, postural hypotension and tachycardia persist during chronic therapy in a small proportion of patients and may necessitate withdrawal of the drug.¹ Postural hypotension necessitated withdrawal of labetalol in three of 16 patients in one series treated with this combined alpha and beta receptor blocking drug and has been a prominent side effect in other recent trials with labetalol. Failure of ejaculation occurs occasionally with labetalol but has not been definitely associated with prazosin or indoramin. The use of indoramin even in low doses as part of a multiple drug regimen is limited by its central depressant action. The other members of this class of drugs uncommonly cause central side effects and their acceptance by patients has been generally good except in the case of phenoxybenzamine.⁴

3 SIDE EFFECTS OF BETA ADRENERGIC RECEPTOR BLOCKING DRUGS. We will not attempt to give a comprehensive description of the side effects of this class which have been well reviewed elsewhere.⁷ However, certain guidelines may be helpful in selecting therapy.

(i) The side effects of beta blockers can be readily predicted for the most part on the basis of their interference with beta receptor mediated sympathetic transmission to the heart, bronchi and peripheral blood vessels. The central nervous and metabolic effects of these drugs are less well understood.

(ii) Since these agents interrupt sympathetic drive to the heart, they should not be used in patients with heart failure, bradyarrhythmias or atrioventricular conduction block.

(iii) All drugs of this class reduce maximal exercise performance and tend to induce mild lassitude. These effects are a consequence mainly of cardiac beta adrenergic blockade although peripheral vasoconstriction mediated by beta 2 receptor antagonism and central nervous depression may be contributory. Beta blockers may prove unacceptable to patients who engage in competitive sports.

(iv) Most other side effects including bronchospasm, peripheral vasospasm and potentiation of hypoglycemia in diabetic subjects appear to

zine. Thus if the addition of relatively small doses of either prazosin or hydralazine fails to achieve blood pressure control it may be necessary to increase the dose of methyldopa, debrisoquine or clonidine above the levels indicated at Step 2.

A further alternative at Step 3 is to substitute labetalol, a combined alpha and beta adrenergic blocking drug for the beta blocker previously administered.

Step 4. This step should be required only in the most resistant cases of severe chronic hypertension associated with evidence of progressive renal, renal or cardiac damage. Two new elements are added: (1) minoxidil, a potent but potentially toxic smooth muscle relaxant drug the use of which is restricted by governmental regulation in most countries (as is that of oral diazoxide which is more toxic and probably not as frequently effective); (2) a dose finding escalation of diuretic therapy with furosemide, bumetanide or ethacrynic acid. The initial dose of minoxidil should be 2.5 mg twice a day increasing, by increments of 2.5 mg twice a day to a maximum of 40 mg/day. Beta blocker therapy is a prerequisite in order to counteract reflex tachycardia. Doses of loop diuretic well beyond the conventional may be required to overcome the tendency to salt and water retention associated with hypertensive nephrosclerosis and minoxidil therapy, in the case of furosemide up to 600 mg twice a day may be required.

Conclusions

The deployment of the newer more selective drugs for the treatment of hypertension can be analyzed from several points of view. Ideally, these drugs should be applied specifically in each case to correct the perturbation inducing hypertension. Because the pathogenesis of most forms of hypertension is not clearly understood such a mechanistic approach is rarely possible at present. However, understanding the mode of action and the side effects of an antihypertensive drug does allow to a limited extent appropriate matching between drug and patient. Even more importantly, it allows the drug to be fitted into a system of stepped care therapy in which antihypertensive agents are combined for synergistic effects. These effects depend upon the correction by one drug of the homeostatic reflexes activated by another and allow the toxicity produced by single agents in high dosage to be avoided.

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guide the choice of options from the following stepped-care system which is summarized in Table V.

Steps 1 and 2 A thiazide diuretic remains the best choice for treating most mild cases of hypertension and as the initial component of stepped care therapy. More potent diuretics may be required for patients with hypertension and renal impairment or congestive heart failure. Until the role of ticrynafen in treating hyperuricemic hypertensive subjects has been established it is probably wisest to withhold diuretic treatment in patients with gout or hyperuricemia and to rely on the use of Step 2 agents.

The reasons for selecting a beta blocker above the alternatives given in Step 2 are twofold. First, the incorporation of agents at Steps 3 and 4 is facilitated by prior beta blockade. Second, the symptoms encountered with beta blocker therapy are usually mild and show little relationship to dose within the conventional therapeutic range (e.g., for propranolol 20 to 480 mg/day). Thus, once therapy with a small dose is shown to be well tolerated, dosage may be escalated with little fear of provoking new side effects. In mild to moderate hypertension, adequate blood pressure control may be obtained by giving medication once per day. In severe cases it should be given twice per day, except in the case of atenolol which has a longer duration of action.² Until more toxicological data have accumulated to show that beta 1 blockers are as safe as the established agents of the non-selective type, they should not necessarily be regarded as having superseded the latter. However, as already outlined, they are preferred in hypertensive subjects with diabetes or peripheral vasospasm. The conventional dose range for metoprolol is from 50 to 400 mg/day and for atenolol it is from 50 to 200 mg/day. Since the dose-response curve for atenolol flattens above 200 mg/day, doses higher than this are not recommended.¹

In patients with heart failure, asthma, or other contraindications to beta blockers, there is a wide choice of alternatives including the three shown in Table V. We do not recommend using any of these agents in maximal dosages as it is usually better to go to Step 3 instead, adding an additional agent. Thus, the dosage ceiling recommended for methyldopa at Step 2 is about 1 gram/day, for appreciable central depressant symptoms are commonly encountered with higher doses. The

Table V A stepped-care system of antihypertensive drug treatment

| | | |
|---|----------------|--|
| Step 1. Diuretic | | |
| Step 2. Diuretic + β blocker | | |
| Or Me hydro | } Low Dose | |
| Or Debrisoquine | | |
| Or Clonidine | | |
| Step 3. Diuretic + β blocker + prazosin | | |
| Or other | Or Hydralazine | |
| Step 4. Loop diuretic + β blocker + minoxidil | | |

ceiling suggested at Step 2 for clonidine is 0.45 mg/day and for debrisoquine it is 20 mg/day. In mild to moderate hypertension only, prazosin (up to 6 mg/day) or hydralazine (up to 100 mg/day) are also suitable alternatives to beta blockade.

Step 3 The prior introduction of a diuretic and a beta blocker allows the commencement of a peripheral vasodilator at Steps 3 and 4 without the development of cardiac stimulation or refractoriness due to secondary fluid retention or hyperreninemia. The synergistic actions of propranolol and hydralazine have been well documented. Although the properties of beta blockers are not as strongly complementary to those of prazosin as they are to those of hydralazine, their hypotensive effects combine with that of prazosin and the following synergistic interactions occur: (1) the tendency for prazosin-induced orthostatic tachycardia is countered by the negative chronotropic action of beta blockers; (2) the blood pressure in the standing position tends to be higher than in the supine position with beta blockers but lower with prazosin; (3) prazosin will prevent the predominance of unopposed alpha-constrictor vascular tone consequent upon blockade of the beta 2 receptor-mediated vasodilator mechanism; (4) beta blockers may prevent the provocation of angina pectoris by prazosin.

In the presence of adequate beta blockade, the dose of prazosin may be increased to 30 mg/day and that of hydralazine to 200 mg/day (or higher in rapid acetylators with normal renal function). However, such doses may not be well tolerated in patients who, because of contraindications to beta blocker therapy, were given one of the other sympatholytic agents at Step 2. Except in regard to the negative chronotropic effect of clonidine, additive but not synergistic relationships exist between these agents and prazosin or hydrala-

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Primary myocardial disease, diabetes mellitus and small vessel disease

In a recent comprehensive study on primary myocardial disease, Shurey and associates included among their group of 133 patients with primary myocardial disease 12 patients with diabetes mellitus. Based on biopsy findings—autopsies were performed in two diabetic patients only—the authors question the possible role of small vessel disease in the pathogenesis of diabetic heart disease. An opposite view was taken by others and by Shurey and colleagues obtained myocardial specimens by ventricular septal biopsy in eight patients with maturity onset diabetes. Coronary angiography performed in four patients was normal in two patients with angina probably normal in one patient with congestive heart failure and with diffuse disease in one patient with cardiomegaly. Focal myocardial fibrosis and varying degree of intimal proliferation of small vessels (30 to 100 microns) were present in all patients. The negative results reported by Shurey and associates may be due to technical difficulties or to the imperfection of the technique. Even the authors felt that it seems difficult to derive from biopsies the prevalence and significance of small vessel disease. Biopsy technique missed focal changes of the myocardium in 3 of 133 patients (2%). The sample obtained by needle biopsy may or may not be representative of the whole.

Therefore autopsy remains the most reliable method in evaluating the changes taking place in the myocardium. We obtained paraffin blocks of 89 hearts from 87 diabetic nonhypertensive patients, and from 3 nondiabetic patients. Four blocks were taken from seven areas. Each block was sectioned at 6 microns and four sections were stained with hematoxylin-eosin and Verhoeff-Van Gieson stain. Small coronary artery involvement (90 to 150 microns) found in 35 diabetic patients (72%) consisted of (1) elastic proliferation (2) subendothelial fibrosis (3) extraluminal deposits of hyaline in the intima and (4) atheromatous plaques with cholesterol clefts and hyalinized intima. Intramural heart vessel involvement alone was found in 18 patients (40%). The vessel involvement alone was found in 18 patients (40%). The heart was enlarged—over 400 g males, and over 375 g females in eight patients with small artery involvement and normal intramural coronary arteries. In the control group of 22 nondiabetic patients involvement of the intramural coronary arteries only was detected in four cases. Since the control group presented a variety of clinical manifestations there is the possibility that intramural vessel involvement was the consequence of underlying clinical disease. The small artery changes are not specific for diabetes mellitus, but are

When is loss of responsiveness to a vasodilator agent in the patient with congestive heart failure due to tachyphylaxis?

One of the subjects of important debate at the recent meetings in Anaheim involved vasodilator therapy for advanced congestive heart failure. Almost 30 years ago dibenamine was shown to decrease right atrial and pulmonary pressure in patients with congestive heart failure and patients with acute pulmonary congestion and edema refractory to conventional therapy were then reported to respond dramatically to the administration of adrenergic or ganglionic blocking agents. Burch and colleagues pointed out that the salutary response in this situation was much more likely to reflect venous distention than afterload reduction. There is continued broad agreement that a beneficial response occurs with the acute administration of a number of additional agents. With attempts at chronic therapy debate now centers on how well sustained responses to individual agents are a recurrent theme appears to be that agents lose their effectiveness with time. Unfortunately the term tachyphylaxis has been employed by some to describe this loss of responsiveness in patients with heart failure providing a contemporary example of how the misuse of word can confuse issues.

When should we employ the term tachyphylaxis rather than the more humble terms refractory, resistant or unresponsive? What additional information does this complicated word carry if any? If it is merely a synonym for refractory or unresponsive we clearly should not use it.

As used in pharmacology tachyphylaxis connotes an element of specificity which unresponsiveness does not. Vascular smooth muscle for example may fail to dilate in response to an agent because the reduced blood flow is not due to active vasoconstriction but rather to some mechanical problem such as edema of the vessel wall, an alteration in excitation-contraction coupling or the contractile apparatus itself so that vasodilatation is not possible. In these cases the refractory state would be generalized and no agent would induce a response. Alternatively response to a specific agent might be lost because of a change in the number or affinity of the available receptors for that agent or because a change in the physiology of the milieu makes the agent ineffective. An excellent example of the latter phenomenon was provided by the studies of Watkins and associates. When acute CHF was induced in the dog converting enzyme inhibition reduced blood pressure strikingly. Over the next several days arterial blood pressure and by inference afterload no longer responded to the inhibition. Plasma renin activity rose sharply following the acute onset of CHF and gradually returned to control value as sodium retention occurred accounting for the resistance of blood pressure to the inhibitor. A similar

sequence could well account for the loss of effectiveness of alpha adrenergic blocking agents. In this case the loss of responsiveness would be specific for a single agent and the system would be capable of responding to other agents. The term tachyphylaxis should be applied to this specific case in which responsiveness is lost to only one agent thus discriminating the loss of response from a generalized refractory state.

This distinction clearly would have important implications for pathophysiology and therapy. Until alternative agents have been assessed and have been shown to be ineffective the term tachyphylaxis should not be applied. One cannot help but wonder how much of the debate would be resolved if we knew whether patients who apparently become resistant to prazosin or hydralazine have indeed become resistant to all agents. Does resistance to one agent preclude effective use of another? Anecdotal, clinical experience indicates that this is not so but none of the formal studies have attempted to answer this important question.

The notion of course applies to other therapeutic maneuvers. Investigators and clinicians involved in the treatment of problems as diverse as cardiac arrhythmia, hypertension, recurrent urinary tract infections, and leukemias often face the problem of the patient whose condition has become refractory to a specific agent—fortunately most have resisted the temptation to replace the general term with tachyphylaxis.

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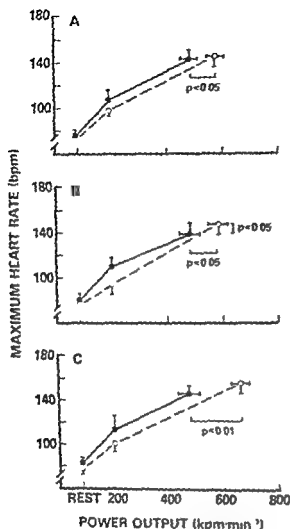


Fig 1 Mean (±1 SD) maximal heart rate and power output (mean ± 1 SD) (A) 0 to 12 months ($n = 17$) (B) 0 to 12 months ($n = 17$) and (C) 0 to 21 months ($n = 7$)

for at least 1 month. 10 patients continued in the program for 12 months, and continued for 21 months. Their mean age (± 1 SD) was 26 ± 8.4 years. 13 had suffered a myocardial infarction (three of whom subsequently had bypass surgery). Two patients had undergone bypass surgery without a prior infarction and two had angina pectoris without infarction or bypass. Exercise testing was carried out on a calibrated electrically stabilized load-cycle ergometer on entry and 7, 12, and 21 months later. Changes in heart rate, systolic blood pressure, rate pressure product, expired ventilation, and power output were analyzed over 0 to 7, 0 to 12, and 0 to 21 months. The exercise program consisted of 30 to 40 minutes of treadmill walking and cycle ergometry, and 20 to 30 minutes of volleyball. The patients met twice weekly and were expected to exercise at home on at least two other days. The intensity of exercise was prescribed by the method of Balke. Supervision was provided by two exercise leaders and a physician.

Following regular participation in the program for as long as 21 months, there were no changes in weight, resting heart rate, but significant ($p < 0.05$) increases were observed in resting systolic blood pressure and rate pressure product by 12 and 21 months. No significant changes were observed in the cardio-

spiratory responses at a constant submaximal power output (200 kpm min⁻¹) at any time, although heart rate at 70 kpm min⁻¹ was lower at each test (0 to 12 months = 145 to 121 bpm; 0 to 12 months = 145 to 121 bpm; 0 to 21 months = 145 to 121 bpm). Significantly higher maximum power outputs (11 to 17) were observed (Fig 1) at the end of 7 months (mean 489 ± 31 to 579 ± 33 kpm min⁻¹) over 12 months (57 to 575 ± 39 kpm min⁻¹) and over 21 months (67 to 671 ± 28 kpm min⁻¹). Maximum heart rate (± 1 SD) increased over each period but significantly only over the 12 month period (138 ± 9 to 144 ± 8 bpm); there were no significant changes in maximal systolic blood pressure, rate pressure product, or expired ventilation at any time.

The proportions of females and males referred to the exercise rehabilitation program were similar to those reported for other programs in North America, and presumably reflect the lower incidence of coronary heart disease in females of perhaps a smaller number of exercising North American middle aged females than males. The dropout rate was somewhat higher than that observed in male cardiac patients exercising at the same institution. The increase in maximal power output and maximal heart rate was similar to that observed in male cardiac patients. The submaximal responses during progressive exercise testing, although not statistically significant, were similar to those reported in the literature for male cardiac patients. The decrease in resting heart rate (a decrease of 12% in submaximal heart rate with a similar exercise prescription (N. Oldridge unpublished data)) All 17 patients claimed that they were able to carry out activities of daily living with greater self assurance and fewer problems than before entering the program. The qualitative subjective improvement in their daily life should be considered at least as important an effect of training as a quantitative improvement found during submaximal work or maximal power output. These observations suggest that physical conditioning plays an important role in the rehabilitation of selected female coronary heart disease patients as well as male patients, particularly in their ability to carry out activities of daily living with a renewed sense of confidence.

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frequency and severity in this disease make them a highly characteristic feature. The small stiff heart causing onset of acute pulmonary edema was reported in diabetic patients when both intramural and extramural coronary arteries were severely involved. Functional derangements in the microcirculation of diabetic patients as a result of small vessel involvement might represent one of the basic causes of myocardial impairment and conduction disturbances.

The changes taking place in the myocardial circulation and metabolic abnormalities, including deposits of PAS material in the left ventricular interstitium might determine progression of the process. A basic departure from the concept—that the myocardial microcirculation in diabetes is different from all the other organs—is taking place. Recently there have been reports describing thickening and proliferation of the capillary basement membrane as a generalized phenomenon taking place in many organs including the heart. For the first time diabetic capillary microaneurysms have been observed in the hearts of three of six diabetic patients.

A protracted period of controversy seems to be approaching its end. The intramural circulation may ultimately be recognized as an important factor in the pathogenesis of diabetic heart disease.

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Exercise rehabilitation of female patients with coronary heart disease

Cardiorespiratory responses to physical conditioning have been extensively studied in male coronary heart disease patients but little information is available for female cardiac patients undergoing similar programs. Twenty eight female

cardiac patients were referred to a supervised exercise rehabilitation program between March 1973 and March 1977 (approximately 8% of male patient referrals over the same time period). 17 of these patients participated in the program

hyperplasia presumably resulting from vasoconstriction has been the basis for vasodilator therapy for primary pulmonary hypertension. Early reports demonstrated pulmonary vasodilatation in pulmonary hypertensive patients who received intravenous infusions of isoproterenol or tolazoline but systemic side effects are common and the clinical usefulness of this therapeutic approach is limited. Only a handful of patients have been reported to obtain benefit from sublingual isoproterenol¹ and the duration of action after each dose is short. Furthermore the absence of any long term follow up of patients treated in this manner speaks of its not being of lasting help over the long haul. Nevertheless the demonstration that the hypertensive pulmonary arterial bed can dilate in response to the administration of vasodilators was encouraging and it initiated a search for more effective and better tolerated pulmonary vasodilators.

Diazoxide, a potent systemic antihypertensive agent has recently been demonstrated to be a pulmonary vasodilator in four patients with primary pulmonary hypertension. In two separate reports^{2,3} diazoxide given intravenously caused a reduction in pulmonary arteriolar resistance and an increased cardiac output without affecting systemic blood pressure. Surprisingly the drug was also effective when administered orally and hemodynamic and symptomatic improvement persisted in the patients who were maintained on chronic oral therapy. This drug however is not given without hazard: a death was recently reported after intrapulmonary diazoxide was given to a patient with primary pulmonary hypertension.⁴

In a recent case report a patient with primary pulmonary hypertension evidenced hemodynamic improvement with the intravenous injection of phentolamine, an adrenergic inhibitor. This patient was treated with oral phentolamine and on repeat catheterization seven months later a persistent response was demonstrated.

We recently reported our experience using oral hydralazine in four patients with primary pulmonary hypertension. In those patients the administration of hydralazine 50 mg by mouth every six hours for 48 hours resulted in a reduction in pulmonary arteriolar resistance and an increase in cardiac output at rest. Similar changes were also observed in three patients who were also studied during a period of exercise on a bicycle ergometer. Repeat cardiac catheterizations were performed four to six months after beginning chronic oral hydralazine therapy and the hemodynamic improvement persisted. Our patients also had symptomatic improvement and this dose of hydralazine was tolerated without significant side effects. Since the publication of our original experience we have had the opportunity to study three additional patients with this disease, two of these had responses comparable to those in our original series.

Despite the inherent risks it is our current practice to perform right heart catheterization before and after instituting hydralazine therapy on all patients who are referred to us with the diagnosis of primary pulmonary hypertension. We have tested our patients for pulmonary vascular responsiveness to the administration of 100% oxygen (seven patients) and intravenous phentolamine (four patients) but we have not found either modality useful.

The temptation to empirically treat pulmonary hypertensive patients with vasodilators must be strongly resisted. Hemodynamic changes may be the only evidence of improve-

ment. It is clear that not all patients will respond to a therapeutic approach and no drug should be given to a patient without the demonstration of both its indication and its efficacy. Systemic hypotension could prove fatal to the often hemodynamically fragile patients. Furthermore vasodilator therapy could augment the right to left intracardiac shunting in patients with pulmonary hypertension resulting from an unsuspected patent foramen ovale and this danger should be used cautiously in this setting.

The demonstration that oral vasodilator therapy could lead to hemodynamic improvement in some patients with primary pulmonary hypertension has raised several important questions:

1. Which vasodilator is the safest and most effective for pulmonary hypertension?

2. What is the optimal dose of a vasodilator for patients with primary pulmonary hypertension? It is now well known that there is a marked variability in the dose requirement of vasodilators for left ventricular failure and undoubtedly a comparable situation exists in pulmonary hypertension.

3. What is the role of concomitant antithrombotic therapy for primary pulmonary hypertension? Although anticoagulation does not appear to cause hemodynamic or symptomatic improvement the increased risk of thromboembolic disease in this setting may be a justification for anticoagulation. Our practice however is currently to withhold anticoagulation unless a clear indication is present.

4. Can the response to vasodilator therapy yield insight into the pathogenesis of this disease? Clarification of the mechanisms of pulmonary vasodilation could not only lead to the discovery of more effective pulmonary vasodilators but it could also provide information concerning the mechanisms of vasoconstriction in the abnormal pulmonary vascular bed.

The answers to these questions will undoubtedly lead to newer approaches to the treatment of this tragic disease.

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Of the Q wave and myocardial infarction

There is an erroneous tendency to assume that only a Q wave abnormality is necessary to establish electrocardiographic diagnosis of myocardial infarction. Thus some clinicians consider that unless a Q wave of infarction is present myocardial infarction does not exist. Nothing could be further from the truth than that concept. Those who subscribe to this concept and so frequently include it in their publications fail to realize that the time course of the Q wave occurs early in the depolarization process of the ventricles. Therefore only infarction in the myocardial area depolarized early in the activation of the electric cycle can be expected to display abnormal Q waves in the ECG. But the QRS complex continues on beyond the Q wave time in the time course of the ventricular depolarization process. Therefore what about infarcts in the areas of the ventricle which are depolarized late and last during the depolarization process? How could these infarcts change the early portions of the QRS complex or produce or change the Q wave? Obviously they don't. Only the late or later parts of the QRS complex are abnormal when infarction occurs in myocardial areas depolarized late in the activation process. This has been clearly shown and reported a number of years ago. Therefore the lack of Q wave abnormalities does

not exclude ECG evidence of myocardial infarction involving those parts of the ventricle depolarized late or last. The absence of a Q wave abnormality only excludes evidence for infarction of areas of the ventricular myocardium depolarized early. Furthermore it should be remembered that infarction of portions of the myocardium depolarized early may produce abnormalities of the early portions of the QRS complex other than the development of Q waves.

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Primary pulmonary hypertension: new approaches to therapy

Thirty years after its original clinical description, primary pulmonary hypertension remains a disease of unknown cause and the few clues to its pathogenesis have not generally led to useful therapeutic modalities. The association of pulmonary hypertension with connective tissue diseases suggests an immunologic or inflammatory process but corticosteroids and cytotoxic drugs have no effect on the course of this disease. Some investigators have postulated that microemboli possibly resulting from a hereditary defect in fibrinolysis cause

the extreme elevations in pulmonary arterial pressures which are often seen in patients with this disease but anticoagulant therapy has not met with success. The exacerbation of pulmonary hypertension during pregnancy and the association of pulmonary hypertension with portal hypertension have led some observers to believe that the disease is the result of a hormonal abnormality. To date however no specific defect has been demonstrated.

The pathologic finding of pulmonary arteriolar muscle

wa.h.a.g.s. While hepatitis B has been transmitted to non human primates by subcutaneous or intravenous injection of HB. Ag positive saliva, intranasal and intra-oral installa- tions did not result in infection. The possibility of HB Ag in saliva reaching the blood of a mouth to mouth operator through small mucoral cracks is suggested by the report of transmission of hepatitis B by a human bite. Although the transmission of hepatitis B after mouth-to-mouth contact of a patient carrying HBs Ag in his blood or saliva has not been reported it would seem prudent to provide mouth-to-mouth contacts of HBs Ag positive individuals with some prophylaxis offered to those exposed to hepatitis B through inadvertent needle puncture from patients known to be HB Ag positive. Such prophylaxis consists of hepatitis B immune globulin given intramuscularly in a dose of 10 mg/kg body weight administered as soon as possible and repeated in 1 day.

Over the last 10 years, there has been expressed about the risk of transmitting hepatitis B via HB Ag positive saliva that has contaminated the mannequin, used to train individuals in CPR. Ozeri and colleagues studied 22 individuals who had participated in a CPR training programme. One of the students developed hepatitis B eight days later and carried HB Ag in his blood and saliva but none of the contacts acquired hepatitis B. There was also no transmission of hepatitis to 23 individual after mouth-to-mouth contact with a CPR mannequin used by the instructor who subsequently developed hepatitis non A nor B. Another fortuitous experiment was the exposure of 12 students to HB Ag positive saliva via contact with contaminated mannequin instruments. All of the instruments were not cleaned between use by the student, and the HB Ag carriers had no transmission of hepatitis B. The results of the CPR training mannequins have been reported in the literature. The transmission of hepatitis B from the mannequin's oral surface to the student's mouth was not observed after each training session.

transmitted from person to person through the upper respiratory tract or through oral secretions of persons although the paucity of reported meningococcal infection by mouth-to-mouth contacts has led some to believe that the risk of such transmission may be small. However, it has been suggested that mouth-to-mouth contacts may be rapid fatal Jacobson and Fraum recommended that mouth-to-mouth contacts of patients with meningococcal infection be given the same chemoprophylaxis as with rifampicin, sulfadiazine or minocycline after close contacts. However there may be a very brief period of colonization of the upper respiratory tract before the onset of meningococcal infection. To eradicate a potentially early bacteremia in the mouth-to-mouth contact Artenstein recommended procaine penicillin in intramuscularly 500,000 units three times daily for two days, followed by orally administered penicillin V 500 mg three times daily for eight days. However Artenstein's regimen may be ineffective because meningococcal infection has been reported in close but not mouth-to-mouth contacts receiving intramuscular procaine penicillin and benzathine penicillin for chemoprophylaxis. When faced with this dilemma I have recommended that the mouth-to-mouth operator be admitted to

hospital and started on 12 million units of penicillin intravenously in divided doses over 4 hours after release from the culture. The mouth-to-mouth operator was discharged two days later if no symptoms developed. If cultures are sterile. Although the approach can seem a bit overzealous, my experience has been that the barrier of the mouth-to-mouth operator allows much of the infection usually engendered by the exposure to a patient with necrotic infection.

The seemingly very small risk of transmission of disease from patient to operator during mouth-to-mouth resuscitation is no reason to abandon mouth-to-mouth resuscitation. However, more frequent documentation of the occurrence of such contacts with patients, harborers of various viruses would allow a better appreciation of the risk involved.

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of viral nephritis

is still doubt in the minds of many physicians and even nephrologists as to whether or not virus will infect kidneys. Viral nephritis due to the Coxsackie B virus has been noted. However it is well known that renal tissue makes a good culture medium for the picornaviruses. The B virus is grown on kidney tissue culture and this is certainly true for other viruses of this same group namely the herpes viruses. This is proof enough that at least the virus affect renal cells.

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hazards of mouth to mouth

as

though it has been suggested that a fear of transmission of infection delayed the widespread acceptance of mouth to mouth breathing in the late 1940s scant attention is currently given to the risks of transmitting infection from patient to rescuer during mouth to mouth resuscitation. The encouragement of prompt cardiopulmonary resuscitation (CPR) by health care people and paramedical personnel in the community will surely result in increasing numbers being exposed to oropharyngeal secretions of patients who may be harboring an infection. Cutaneous tuberculosis and meningococcal infection have been described in operators of mouth to mouth resuscitation of patients with these diseases. One can only speculate about the potential for transmission of other microorganisms during mouth to mouth resuscitation. The risks of transmitting hepatitis and meningococcal infection deserve

special attention not only because of the potentially serious consequences of the infection but also because the management of such mouth to mouth contacts is debatable.

Oropharyngeal secretions are not an important source for transmission of hepatitis A virus while hepatitis B is most likely to be transmitted by the parenteral route via blood blood products or blood drawing equipment. However the mouth-to-mouth route of transmission of hepatitis B is theoretically possible by two mechanisms.

1. Hepatitis B has been transmitted to children by the oral administration of as little as 0.5 ml. of hepatitis B surface antigen (HBs Ag) positive serum. Thus bleeding about the oropharynx of the patient may result in blood containing HBs Ag being swallowed by the mouth-to-mouth operator.

2. HBs Ag may be found in both saliva and nasopharynx.

increased incidence of prematurity (22% one third of whom died) and stillbirth (13%). While liveborn morbidity was much less, fetal or neonatal death was substantially greater with heparin use than with coumarin derivative exposure. In addition, maternal risk may be greater with heparin use (at least as previously administered).

Both of these agents carry substantial risks when used in pregnancy. Because of this, preconceptual counseling and if pregnancy occurs, offering the option of therapeutic abortion appear to be the most prudent. If anticoagulation and continuation of pregnancy are necessary, the clinician is left to choose between unattractive alternatives. Continued experience may demonstrate that heparin is in fact safer than our retrospective review would indicate. For the present, however, coumarin derivatives remain a reasonable alternative if the relative risks are explained carefully to the prospective parents.

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of anticoagulation during pregnancy

The recognition that coumarin derivative oral anticoagulants have adverse effects on the fetus has followed a tortuous path. The increased sensitivity of offspring to the hemorrhagic effect of the active principle of damaged sweet clover was noted more than 40 years ago, and hemorrhagic complications in human newborns resulted in general recommendations that these agents (including Coumadin [Endo Laboratories]) should not be used in the latter part of the third trimester of pregnancy.

In the last five years we and others have demonstrated coumarin derivative exposure in the first trimester of pregnancy results in a specific malformation syndrome in infants which has come to be known as the warfarin embryopathy. We are aware of 39 infants with the warfarin embryopathy which is characterized by nasal hypoplasia and epiphyseal dysplasia. Review of exposure histories in these cases indicates that there is a critical period of exposure between six and nine weeks of gestation that can result in the appearance of the warfarin embryopathy. The severity of this syndrome is variable; follow up studies indicate that while seven subjects died, most survivors have a relatively good outlook with little or no severe disability at all.

Our recent review also summarizes experience with central nervous system effects of coumarin derivative exposure in utero. Administration of these agents in the second and third trimester appears to be associated with deformation of the central nervous system, resulting in mental retardation and/or blindness. A total of 15 such cases were found. While some children have had both the embryopathy and central nervous system abnormalities, these appear to be two independent processes with different sensitive periods during gestation and different mechanisms of pathogenesis and with independent additive risks.

So coumarin derivative exposure in the sixth to ninth weeks of the first trimester carries some risk for the warfarin embryopathy, exposure in the second and/or third trimesters with increased incidence of central nervous system abnormalities, and late third trimester exposure car-

ries with a clearly recognized danger of late prenatal, perinatal or postnatal hemorrhage.

Nevertheless, use of anticoagulants during pregnancy may be necessary because of maternal thrombophlebitis with embolization or maternal prosthetic heart valves. Counseling of such women requires estimation of the involved risks. The most satisfactory approach would be a prospective controlled trial but no such trial has been undertaken and since the coumarin derivatives are now contraindicated during pregnancy by their manufacturers, none will probably be forthcoming. Yet some estimate needs to be available. After an unsuccessful attempt to retrospectively ascertain all women given anticoagulants during pregnancy in the Seattle-Washington area over the past ten years, we chose to review the world's literature from 1945 through 1978 attempting to find all published cases of coumarin derivative (and for comparison heparin) use during pregnancy. The limitations and biases of such a study should be evident; therefore our risk figures must be considered as estimates. For coumarin derivatives, 418 literature cases were reviewed. Over all, only two-thirds of these pregnancies resulted in reasonably normal fetal outcome. Abnormalities in the others were primarily secondary to hemorrhage: warfarin embryopathy, central nervous system effects, and spontaneous abortion. In at-risk pregnancies (exposure between six and nine weeks of gestation) about 8% of infants were reported to have features of the embryopathy. The overall risk of central nervous system effects appears to be about 3%. Of liveborn infants, 16% had some significant sequelae. So the best available estimates indicate that with coumarin derivative use one-third of pregnancies will result in abnormal liveborn infants, one-sixth will end in abortion or stillbirth, and about two-thirds will have a relatively normal outcome.

Data from 130 published cases in which heparin was used during pregnancy indicate a virtually identical complication rate: less than two-thirds of such pregnancies resulted in normal children. The kinds of problems, however, were quite different: heparin use was associated for the most part with

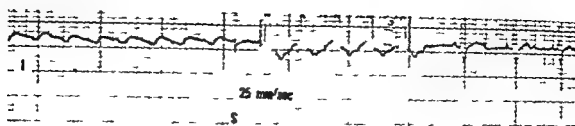


Fig 1 Ventricular tachycardia with a rate of 140 per minute terminated after six ventricular stimulations at a rate of 110 per minute

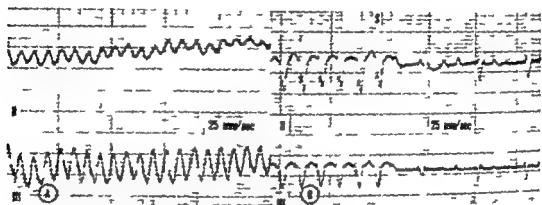


Fig 2 Simultaneous recording of Leads II and III. A ventricular flutter with a rate of 260 per minute. B ventricular stimulation at 200 stimuli per minute and then sinus rhythm with a 1:1 block.

interrupted the reentry circuit, allowing the others to drive the atrium, and after the last stimulus sinus rhythm occurred.

The same mechanism was observed in a 70-year-old woman with total A-V block and bursts of ventricular tachycardia and ventricular flutter unresponsive to repeated DC shocks. The ventricular stimulation below the rate of ventricular tachycardia (Fig 1) and below the rate of ventricular flutter (Fig 2) succeeded in driving the ventricles and finally in stopping the arrhythmia. A permanent ventricular pacemaker was effective in preventing these arrhythmias and the patient was in satisfactory condition at a follow up examination 3 months later.

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TTM versus Holter monitoring of symptomatic arrhythmias

To the Editor

In their article in the October 1979 issue of the *Journal* (AM HEART J 98: 459, 1979) Dr R. S. Grodman and associates pointed out that the value of a patient activated telephone transmission system (TTM) was statistically

Dynamic electrocardiographic recording during sexual activity in recent post myocardial and revascularization patients

To the Editor

We greatly appreciated the article of Johnston and Fletcher which appeared in the December 1979 issue of the AMERICAN HEART JOURNAL, and we would like to make some comment on it.

At the moment in our Cardiac Rehabilitation Center we focused our attention only on post myocardial infarction patients (post MI Pts).

Sixty nine post MI Pts, 26 randomly assigned to a physical

and 27 to a control group and 16 excluded from randomization for cardiovascular contraindications, performed 85 24 hour ambulatory electrocardiograms during which there were 86 occurrences of sexual intercourse.

The time lapse from MI was 49.6 ± 10.3 days, ages, ranged from 30 to 64 years ($X = 49$) the infarction was inferoposterior in 41 and anterior in 28 patients.

Total time for sexual activity ranged from 8 to 28 minutes ($X = 16.5$) and we included in the analysis 10 minutes before and 10 minutes after that event. Peak heart rate ranged from 110 to 170 beats per minute ($X = 108$).

Ventricular ectopic activity (VEA) was graded according to the Lown system integrated with a study of bigeminy and trigeminy and has been expressed as percent of hours with a certain degree of VEA. A total of 1 092 daily hours of sexual activity have been reviewed.

86 instances of sexual intercourse have been reviewed. During hours have not been included. Total VEA and uniform extrasystoles were increased although not significantly during sexual activity (SA). The most striking difference regarded the advanced grades of VEA, namely complexes, and bigeminy and trigeminy that

all significantly more frequent during SA ($P < 0.025$).

A further analysis comparing sex with other daily activities as driving, climbing stairs, light manual work, prandial post prandial state awakening etc., showed that although SA elicited more advanced grades of VEA the difference was not statistically significant.

In our total population of 263 patients under study we have observed many "mood changes". In conclusion, in our experience sexual activity in the early post hospital phase of MI is not clearly a stronger stimulus than are other activities and cardiac electric instability. Even if we agree that appropriate counseling should obviously be expressed regarding activity in this phase of patient management excessive activity seems to be inappropriate and may create psychological problems.

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Reply

To the Editor

We appreciate the interest shown in our study by Drs. Paolillo and associates. It appears as though both groups of data are quite comparable. However, Paolillo and co-workers studied only patients with myocardial infarction and at a time of 49.6 days post infarction. Our myocardial infarction patients were monitored at an earlier mean time of 30.1 days post infarction. This earlier "time frame" for monitoring could possibly account for the fact that one myocardial infarction patient experienced ventricular bigeminy and ventricular coupling during sexual activity and not during other activities within his 24 hours. However, the higher grades of ventricular ectopic activity (VEA) detected by Paolillo and colleagues, even at a later time post myocardial infarction, should be of concern. We concur that counseling should not be such as to incite "alarm" in the patient and partner. However, the apparent relationship between the incidence of sudden death and high grade VEA in patients with ischemic heart disease does warrant consideration of therapeutic approaches that are tailored for the benefit of the individual subject in question.

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Pacing below the ventricular rate in terminating ventricular tachycardia and flutter

To the Editor

Short bursts of ventricular stimuli at about 300 per minute or programmed ventricular premature beats, allowed termination of medically refractory recurrent ventricular tachycardia. **

In a former paper on atrial flutter using a stimulation below the atrial rate we have found that the first stimulus

exist a small group of patients whose infrequency and short duration of symptoms will defy ECG documentation by the above methods i.e. the white field of Weber and associates. Perhaps this group of patients is better studied by a long term limited usage patient actuated Holter type recording system as a further adjunct to standard HJM and TTM.

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Ratios of septum and LV free wall in IHSS and HCM

To the Editor

Idiopathic hypertrophic subaortic stenosis or hypertrophic cardiomyopathy is characterized by asymmetric septal hypertrophy (ASH), myocardial fiber disarray and often systolic anterior motion of the mitral valve (SAM). Although these findings are highly suggestive, however, none of them are pathognomonic for this fascinating disorder. ASH (a ratio of the septum to posterior left ventricular free wall of ≥ 1.3) has been reported in normal embryonic and newborn hearts as well as in certain congenital heart disorders. While studying embryonic chicken hearts for a teratologic project, we conducted a (quantitative) morphometric investigation on three groups of white Leghorn chicken hearts (8 day old embryos, 1-day old chickens and adult specimens). Serial sections parallel to the frontal plane were obtained from 10 hearts in each group and were stained with hematoxylin and eosin. Sections containing the ventricular septum, medial leaflet of the mitral valve and the aortic root were used for morphometric study (Fig. 1). A line (A) was drawn parallel to the longitudinal axis of the ventricular septum. Perpendicular lines were dropped to line A at three points (dividing line A into four equal portions) and were extended laterally to cross the left ventricular free wall. The length of the line A was determined by the aortic root (RV) superiorly and its point of intersection (X) with line III passing tangentially to the

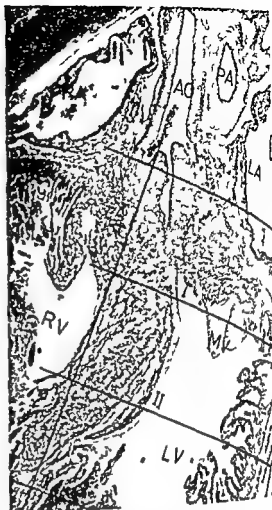


Fig. 1 A typical frontal section of chicken heart contains the aortic root (AO), the medial cusp of the mitral valve (MV) and lines drawn for measuring septal to left ventricular wall thickness ratio at three equidistant levels (I, II and III). Line II is not shown in the Figure. LA = left atrium, LV = left ventricle, PA = pulmonary artery, RA = right atrium, RV = right ventricle.

lowest part of the left ventricular wall. Ratios of the septal thickness to the left ventricular wall were measured at three levels for the three groups and were compared using the hypothesis on mean \pm SD of each group (Table I). The results showed that:

1. The ratio for the upper portion (level I) of the septum to left ventricular free wall is quite large in the embryonic group and this ratio is rapidly reduced so that in 1-day old chicks the upper ratio has reached the adult level and does not change further with advancing age.
2. The ratio for the middle portion (level II) declines gradually so that in 1 day old chicks it is not significantly less than in the 8-day-old embryos; however, as the chicks mature this ratio is gradually reduced and becomes significantly smaller in the adult specimens.
3. The ratio for the lower portion (level III) though reduced with advancing age is not significantly different among the three groups.

RECOGNITION OF SYMPTOMATIC ARRHYTHMIAS

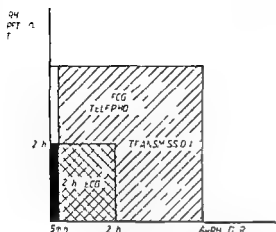


Fig 1 Diagram illustrating the overlapping coverage of symptomatic arrhythmias provided by the use of both TTM and 24 hour Holter monitoring. Short lasting symptomatic arrhythmias (< 5 min i.e. mean TTM-connection time) of high reoccurrence frequency (> 1 phenomenon/day) could only be captured using HT (pure black field) whereas rare arrhythmias (< 1 /day) will remain undiscovered in spite of application of both methods used (pure white field)

significantly higher ($\chi^2 = 3.69$ $p < 0.05$) than the analysis of one 24 hour Holter tape (HT).

But the truth is that each method brings different strengths to the problem of capturing symptomatic arrhythmias. It is important to understand that the sensitivity of HT and TTM depends on the frequency of the occurrence of symptoms vs. arrhythmias. In 97 symptomatic patients—in spite of mean 4 days (maximum 21 days) continuous monitoring—under ambulatory conditions—a symptom/ECG correlation could be achieved in only 40 patients. Using computer supported HT analysis systems the analysis of synchronous registration of ECG and symptoms leads to the true result independent of the duration of the phenomenon.

On the other hand a successful application of TTM (i.e. a simultaneous ECG registration of a symptomatic period) presupposes that there will be a telephone connection between the patient and the receiving unit before the symptoms ensue.

So we conclude that the value of HT analysis depends on the frequency whereas the value of TTM is a function of the duration of symptoms vs. arrhythmias. A disregard of the duration and frequency of symptoms shows a lack of understanding of the value of each method.

Both methods are useful tools with which to reduce the white field (see Fig 1) of undiscovered symptomatic arrhythmias by the use of overlapping data.

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Reply

To the Editor

We thank Drs. Weber, Steinbach, Joskowicz, Glogar, and Kaundl for their interest in our article. We agreed that the sensitivity of Holter monitoring (H.M.) and transtelephonic monitoring (T.T.M.) is a function of the frequency and duration of symptoms and arrhythmias.

The efficacy of H.M. is truly limited by the frequency of the patient's symptoms. It is less likely to document symptom-related arrhythmias in the sporadic patient than in the highly symptomatic patient. This is exactly the reason we sought to test T.T.M. as an alternative to H.M. in this situation. T.T.M., on the other hand, is duration limited, i.e. an arrhythmia must be present at the time of the transtelephonic transmission in order to be documented. In addition, a sustained critical arrhythmia may render the patient incapable of transtelephonic transmission, thereby losing the opportunity for symptom/ECG correlation. We have recognized these conditions and listed them in our discussion, as did Hasin and colleagues and Judson and co-workers in their studies on the usage of T.T.M.

We believe it is important when correlating symptoms with the transmitted ECG to have the patient relate by telephone whether or not symptoms were actually occurring during the period of ECG transmission. This will eliminate one source of symptom/ECG disparity. Also, by extending the time period for the use of T.T.M., it will be more likely that a truly symptomatic period can be recorded, further improving the sensitivity of the method.

Weber and associates note that a period of continuous ECG ambulatory monitoring of 4 days (mean) duration, with a maximum continuous recording period of 21 days, can achieve a high incidence of recording during symptoms, and a high symptom/ECG correlation. This frequent application of continuous recording is appropriate for investigative purposes, but is neither practical nor possible in the routine care of patients. Thus, effective therapeutic efforts must depend on either a single or perhaps two 24-hour Holter recordings, or must seek other techniques for documentation of the patient's ECG at the time of potential cardiac symptoms. We believe that the T.T.M. has emerged as one method of achieving this goal.

Finally, we stated that T.T.M. both complements and supplements H.M. in symptomatic patients. There still will

We note also that Case 2 was not described as having an abnormal mean frontal QRS axis on the electrocardiogram whereas five of the six patient described by Ehlers and associates had a superiorly orientated axis, and thus has also been our experience (Duncan W J., unpublished observations). Is there any further evidence not mentioned in the article that might suggest that Case 2 does in fact have eccentric left ventricular hypertrophy rather than an aneurysm?

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Reply

To the Editor

We appreciate the comments of Dr Burns and colleagues regarding Case No 2 in our recent communication. Our Case No 2 did not demonstrate the electrocardiographic abnormalities seen by Ehlers and associates in patients with eccentric left ventricular hypertrophy. The mean frontal QRS axis was +30 degrees and there was normal progression of the R wave in all precordial leads. Furthermore an echocardiogram obtained at the age of 13 years when the patient weighed 95 pounds demonstrated the thickness of the interventricular septum as well as the left ventricular posterior wall to be 8 mm. A chromosomal analysis has not been done but the patient has no abnormal features to suggest any syndrome. Therefore we feel that this case demonstrates a left ventricular aneurysm rather than eccentric left ventricular hypertrophy of the left ventricle.

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Anomalous ECG and PCG recordings

To the Editor

In the article by Drs. Lofty L. Basta and Jerry J. Berry (*AM HEART J* 97:96 1979) on page 108, in Fig 18, the left parasternal cardiogram and the phonocardiogram were to have some mistakes. If the figure is placed correctly, points 1 in the parasternal cardiogram and 9 in the phonocardiogram are labeled incorrectly because each of them precedes the QRS complex in the ECG. On the other hand, the S-S interval being longer than the S-S interval is peculiar.

I think that this figure should be placed upside down; then one could see the positive P wave with a P-R interval of 0.25 sec. in the ECG, the S-S, greater than S-S, and the first S in the PCG and point E after the QRS and a large, wide positive outward movement in the parasternal cardiogram.

I would appreciate it very much if you could reevaluate the matter.

Tarkan Gurel MD
Department of Cardiology
Ankara University
School of Medicine
Ankara Turin

Reply

To the Editor

The authors appreciate Dr. Gurel's comments and are clearly see Dr. Gurel's point.

However this particular recording is obtained from a patient with left bundle branch block and marked intraventricular conduction delay. The initial part of the QRS as seen in the ECG lead recorded. In fact, it was about 0.05 sec earlier than the first upward deflection seen in this particular lead. Furthermore we believe S₁ in this figure is the aortic component of the first heart sound recorded in the left parasternal area whereas the S₂ is the aortic component of the second heart sound which is considerably delayed in time because of left bundle branch block, accounting for the long S₁-S₂ interval.

Lofty L. Basta MD FACP
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Clinical Director of Cardiology
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Clinical Professor of Medicine
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able 1 Mean values and SD of septal/left ventricular free wall thickness ratios at three levels in the three groups of hearts

| | Level 1 | Level 2 | Level 3 |
|--------------------------------|----------------|----------------|----------------|
| Group I 8-day-old embryos | 1.6144 ± 0.516 | 1.3660 ± 0.259 | 1.1440 ± 0.163 |
| Group II 1-day old chickens | 1.0625 ± 0.143 | 1.030 ± 0.260 | 1.2400 ± 0.347 |
| Group III adult hearts | 1.0590 ± 0.129 | 0.946 ± 0.133 | 0.956 ± 0.240 |
| ■ values | | | |
| I vs III | < 0.01 | < 0.001 | Nb |
| I vs II | < 0.01 | NS | Nb |
| II vs III | NS | < 0.01 | Nb |

b = not significant

As the septal to left ventricular free wall ratio may be deduced by septal thinning or left ventricular free wall thickening it may be stated that either the ventricular septum thins out rapidly at the upper level more slowly at mid level and not at all at the lower level or the left ventricular free wall thickens more rapidly at the upper level more slowly at the mid level, and not at all at the lower level. Studies are in progress aimed at answering this question in more detail however preliminary evaluation of results shows that both factors are simultaneously operative.

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Fig 1 Left ventricular angiogram in diastole of a patient with eccentric left ventricular hypertrophy

LV hypertrophy versus aneurysm?

To the Editor

We enjoyed the article "Congenital aneurysms of the left ventricle" by Dr Singh and associates and we have one important question to raise. In the angiograms shown by Dr Singh and colleagues, we agree that three of the four cases showed convincing aneurysms of the left ventricle. With regard to Case 2 however we were struck by the resemblance of the left ventricular outline to that seen in eccentric left ventricular hypertrophy as described by Ehlers and co-workers. We also have seen this particularly in patients with Noonan's syndrome. We include a diastolic frame from such a left ventricular angiogram (Fig 1) which shows the similarities. In systole the apical segment did not contract paradoxically.

We note also that Case 2 was not described as having an abnormal mean frontal QRS axis on the electrocardiogram whereas five of the six patient described by Ehlers and associates¹ had a superiorly orientated axis and this has also been our experience (Duncan W J., unpublished observations). Is there any further evidence not mentioned in the article that might suggest that Case 2 does in fact have eccentric left ventricular hypertrophy rather than an aneurysm?

J E Burns
J A G Culham
W J Duncan

From the Division of Cardiology of the
Department of Pediatrics and the
Department of Radiology
Hospital for Sick Children
Toronto Ontario Canada

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- 1 Singh, A., Katkov H., Zavoral J H., Sane S M., and McLeod J D Congenital aneurysms of the left ventricle *AM HEART J* 99 25 1980
- 2 Ehlers, K H., Engle M A., Levin A R., and Deely W J Eccentric ventricular hypertrophy in familial and sporadic instances of 46 XX XY Turner phenotype *Circulation* 45 639 1972.

Reply

To the Editor

We appreciate the comments of Dr Burns and colleagues regarding Case No 2 in our recent communication. Our Case No 2 did not demonstrate the electrocardiographic abnormalities seen by Ehlers and associates in patients with eccentric left ventricular hypertrophy. The mean frontal QRS axis was +30 degrees and there was normal progression of the R wave in all precordial leads. Furthermore an echocardiogram obtained at the age of 13 years when the patient weighed 9½ pounds demonstrated the thickness of the interventricular septum as well as the left ventricular posterior wall to be 8 mm. A chromosomal analysis has not been done but the patient has no abnormal features to suggest any syndrome. Therefore we feel that this case demonstrates a left ventricular aneurysm rather than eccentric left ventricular hypertrophy of the left ventricle.

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- 1 Singh, A., Katkov H., Zavoral J H., Sane S M., and McLeod J D Congenital aneurysms of the left ventricle *AM HEART J* 99 25 1980
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To the Editor

In the article by Drs Lofty L. Basta and Jerry J. Berry (AM HEART J 97:96 1979) on page 108 in Fig. 18, the left parasternal cardiogram and the phonocardiogram seem to have some mistakes. If the figure is placed correctly in the parasternal cardiogram and S in the phonocardiogram are labeled incorrectly because each of them provides the QRS complex in the ECG. On the other hand, the S-T interval being longer than the S-S interval is peculiar.

I think that this figure should be placed upside down. In one could see the positive P wave with a T-R interval of 12 sec in the PCG the S-S greater than S-T and the first in the ICG and point E after the QRS and a large and positive outward movement in the parasternal cardiogram.

I would appreciate it very much if you could reveal this matter.

Turhan Gurel, M.D.
Department of Cardiol
Ankara University
School of Medicine
Ankara, Turk

Reply

To the Editor

The authors appreciate Dr Gurel's comments and clearly see Dr Gurel's point.

However this particular recording is obtained from patient with left bundle branch block and marked intraventricular conduction delay. The initial part of the QRS is seen in the ECG lead recorded. In fact it was about 0.06 s earlier than the first upward deflection seen in this particular lead. Furthermore we believe S in this figure is the transverse component of the first heart sound recorded in the left parasternal area whereas the S₂ is the aortic component of second heart sound which is considerably delayed in this case because of left bundle branch block, accounting for the S-S interval.

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book reviews

Cardiac Rehabilitation for the Practicing Physician Edited by Lenore R Zohman M.D. and Albert A Kattus M.D. St Louis 1988 The C.V. Mosby Company 124 pages

This is a 124 page book on a subject which is relatively new in cardiology. All physicians responsible for patients with heart disease are primarily responsible for rehabilitation of their patient. The book reviews briefly the concepts in practice today. The nine parts include general discussions, psychological considerations, work and job rehabilitation and placement, exercise programs, risk factors, sexual activity and other aspects of rehabilitation of patients with myocardial infarction. The many contributors express their views clearly and effectively. This is the second volume of a series of volumes under the editorship of Dr Zohman. These papers are presented at a symposium held during March 1987. Physicians in practice will find these discussions to be useful and interesting especially if they have never considered cardiac rehabilitation seriously. The increasing interest in this subject makes this publication important. It is practical and is needed at the busy practicing clinician with little time for study.

Exercise Electrocardiography: Practical Approach Edited by Edward K. Chung M.D. F.A.C.C. Baltimore 1979 The Williams & Wilkins Company 354 pages Price \$30.00

This book on exercise testing electrocardiography, edited by Dr Chung and 13 contributors reviews exercise testing techniques and principles. The problems related to the use of exercise testing are discussed. Indications, contraindications, interpretation of data, values in screening for heart disease and complications are among the subjects discussed. Because of the use of exercise testing physicians who use and rely on this procedure in clinical practice will find this book interesting and especially useful for physicians in training. The illustrations are good and the presentations of bibliographies are helpful. This is not a book in which to find a concise critical discussion of the need for exercise testing, dangers, value and limitations of exercise testing. Nevertheless, the use and practices at present are described. The reader will have to provide for himself as to the usefulness of the book to him.

Deep Vein and Arterial Thrombosis Edited by J. Heinrich Joist M.D. Ph.D. and Laurence A. Sherman M.D. New York 1979 Grune & Stratton Inc 373 pages Price \$18.50

This is a new publication on an old important clinical problem. It represents a series of reports from a symposium held on April 6 and 7, 1978. The contributions include among many aspects of thrombosis pathogenesis, diagnosis, pulmonary embolism, prevention, mechanism of action of heparin and coumadin, role of thrombolytic therapy, myocardial infarction, cerebrovascular occlusive disease, use of radioisotope detection and platelet suppressant therapy. This publication provides a good single source on the subject of thrombosis. It includes current concepts and interests. It is a useful book for clinicians, surely for cardiologists.

Advances in Microcirculation: The Microcirculation in Diabetes Edited by E. Davis and B. M. Altura and H. J. Bander. Basel 1979 S. Karger AG 157 pages Price \$81.00

This is volume 8 of *Advances in Microcirculation*. Changes in the small vessels in diabetes though known to exist for many years remain a great puzzle in medicine. This important publication of 157 pages is extremely interesting. Among

the subjects discussed are hemorrhheology, basal lamina in capillaries, management of leg ischemia and vascular smooth muscle. The discussions are concerned with pathogenesis, pathology and clinical diagnosis and management. The relationship of diabetes to the vascular lesions is discussed effectively. This is another important and timely volume on the microcirculation.

Current Cardiology vol. 1 Edited by M. Irene Ferrer M.D. Boston 1979 Houghton Mifflin Company 384 pages Price \$30.00

This is volume 1 of *Current Cardiology* the series to be edited by Dr Ferrer. The purpose of these annual volumes is to make available the changes in cardiology to the practicing physician and cardiologist as they occur each year. The 19 chapters in this volume include a discussion of hypertension, valvular heart disease, coronary artery disease, pediatric cardiology, ventricular function, arrhythmias, pacemakers, the cardiac cell, echocardiography, cardiac surgery, cardiovascular pathology, and other subjects. The presentations are too brief to be comprehensive enough to inform the reader adequately of the subjects selected for discussion. Some of these problems selected are complex and currently there are differences of opinion concerning the mechanism and pathophysiology involved and they need future study. This is well exemplified by the chapter on the use of vasodilators for CHF. Starling's law of the heart, the role of the peripheral circulation and the nervous system is too extensive a field to discuss in about 11 pages. This is also true for the broad field of cardiovascular pathology, which is presented in less than 20 pages. Regardless, the discussions are interesting and present current views in cardiology. These views are discussed in a critical manner. It is hoped in future volumes that either fewer subjects are selected for more thorough and critical review or that the subjects selected be more specific. There is a need for critical evaluation and review and discussion for the reader of current practices and concepts in cardiology. This is especially important for the reader who is less informed and trained and who needs a critical evaluation of current concepts and practices in cardiology.

Hemodynamics and the Blood Vessel Wall Edited by William E. Stehbens, M.D., Springfield Ill. 1979 Charles C. Thomas, Publisher 646 pages Price \$68.50

This is an important book. Hydraulic engineers have developed the fundamental principles of fluid flowing through rigid tubes, whereas blood vessels are not rigid and blood is a non-Newtonian fluid. The hydraulic principles governing the flow of blood through small and large blood vessels depend upon different factors related to the elasticity of the wall, the distensibility of the vessels, the changing tone and other complex factors. These and many other hemodynamic and physiologic phenomena are discussed by the several contributors. Blood flow in vessels in association with certain disease states such as aortic stenosis, aneurysms, A-V shunts and arterio sclerosis are discussed.

Stehbens, a pathologist, has nicely related morphologic, normal, and pathologic states to hemodynamic phenomena. The book is a good one which should interest pathologists and physiologists. It is unlikely that practicing physicians will appreciate the book fully. There has been a need to describe in a single volume for the convenience of others the relationship of the physiologic and morphologic characteristics of hemodynamic phenomena.

Fourth Annual National Symposium on Aging

The Fourth Annual National Symposium on Aging will be held on November 15 and 16 1980 at the Golden Gateway Holiday Inn San Francisco. Devoted to a review of health care needs of the elderly sessions will center on a description of health care for older people and a review of the resources available. Specific and prevalent problems in geriatric medicine will be examined such as the aging heart stroke and the older patient cancer and aging and depression and disengagement among the elderly. Ultimately the recommendations of this symposium will be included in the 1981 White House Conference. Fee for the symposium is \$90 and AMA credit is available. For further information contact Continuing Education in Health Sciences University of California San Francisco 24 Kirkham San Francisco Calif 94143 Telephone (415) 668 3904.

Clinical Recognition and Management of Heart Disease 1981

The 24th Annual Scientific Session of the American Heart Association, Arizona Affiliate will be held on January 21 through 24 1981 at the University of Arizona Health Sciences Center Tucson. The seminar is entitled "Clinical Recognition and Management of Heart Disease 1981." Visiting faculty will include Robert S Eliot M.D., University of Nebraska; Michael S Gordon M.D. Ph.D. FACP University of Miami School of Medicine; Donald C Harrison M.D., Stanford University; and Douglas P Zipes, M.D., Indiana University. Emphasis will be placed on bedside observation and auscultatory skills stressed through the use of the Cardiac Patient Simulator. The lectures will deal with the management of cardiovascular problems with special reference to new pharmacologic approaches and modes of therapy. Comprehensive audiovisual presentations are planned and the course has been structured to permit participants to explore areas of individual interest in depth.

For further information write Gordon A Ewy M.D. Professor of Medicine Course Co-Director Dept. of Internal Medicine Section of Cardiology Health Sciences Center University of Arizona Tucson Ariz 85724.

Society for Clinical Trials Symposium

A Combined Annual Scientific Sessions of the Society for Clinical Trials and the Eighth Annual Symposium for Coordinating Clinical Trials will be held May 11 through 13 1981 in San Francisco California. Sessions will focus on the design organization management and analyses of clinical trials. Abstracts must be received by January 1 1981. For further information write Christian R Kohn M.D. Secretary Society for Clinical Trials Inc. 600 Wyndhurst Ave. Baltimore Md 21210.

Lucien Dautrebande Pathophysiology Prize-1982

The "Fondation de Physiopathologie Professeur L. Dautrebande" will hold its next competition for the Dautrebande Prize in 1982 and the award will be approximately 1 400 000 Belgian francs. The award will be given for a work in human or animal clinical physiopathology preferably having therapeutic implications. For further information about the competition please write: Office Fondation de Physiopathologie Professeur Lucien Dautrebande 35 chaussée de Lagny 5200 Huy Belgium. For consideration in the 1982 competition all papers must be received before December 31 1981.

Second Banff Hypoxia Symposium

The Second Banff Hypoxia Symposium sponsored by The Arctic Institute of North America will be held at the Fairmont Hotel, Banff Alberta Canada on January 11 through 17 1981. The program is designed to interest clinicians and research workers. A special session on January 11 will be devoted to the diagnosis management and prevention of altitude illness. Registration for the four-day symposium is \$150 or \$120 if paid by December 1 1980. A maximum of persons will be accepted. For further information contact John R Sutton M.D. The Arctic Institute of North America, The University of Calgary 200 University Drive N.E. Calgary Alberta Canada T2N 1N4 Telephone (403) 243 3387.

Conference on Coronary Artery Bypass Surgery

The National Heart Lung and Blood Institute (NHLBI) in collaboration with the Office for Medical Applications of Research (OMAR) National Institutes of Health, and the National Center for Health Care Technology (NCHCT) are sponsoring a Consensus Development Conference on Coronary Artery Bypass Surgery to be held on December 5 through 5 1980 at the National Institutes of Health Bethesda Md. The conference will focus on the clinical and scientific aspects of coronary artery bypass surgery. A major conference emphasizing the economic societal and medical aspects of the procedure will be sponsored in Spring 1981 by the NCHCT with the collaboration of NHLBI and OMAR. For further information regarding the December conference contact Nance McManus, Prospect Associates, 11225 Seven Locks Rd., Potomac MD 20854 Telephone (301) 943-6200.

Books received

Recording EKG's in Infants and Children By J. A. Harris
A. R. Feinstein Boston 1979 Little Brown & Company
pages Price \$12.50

Heart Valves By Marian I. Ionescu MD FACS
Mass. 1979 Butterworths, USA 373 pages Price
\$100

Diabetes and Hypertension Edited by Philippe Meyer
and Henri Schmitt New York 1979 John Wiley & Sons Inc
272 pages Price \$42.50

Clinical and Laboratory Haematology (Journal) Edited by J
England Oxford 1979 Blackwell Scientific Publications

Death and Psychiatric Illness By Martin H. Wend
MD Jamaica, N. Y., 1979 Spectrum Publications Inc
9 pages Price \$30.00

Vascular Function: Principles and Applications By
L. Abel MD, PhD and Ernest P. McCutcheon
MD Boston 1979 Little Brown & Company 411 pages
Price \$35.00

**Advances in Experimental Medicine and Biology: Dynamics
of Arterial Flow** Vol. 115 Edited by S. Wolf and N. T.
Werthessen New York and London 1979 Plenum Press 472
pages Price \$47.50

Enzymes in Cardiology: Diagnosis and Research Edited by
H. J. Hearse and J. DeLeurs New York 1979 John Wiley &
Sons Inc 5.6 pages Price \$40.00

Ischemic Heart Disease By I. A. Shkhvatsava St. Louis
1979 The C. V. Mosby Company 413 pages Price \$17.50

Controlling the Smoking Epidemic World Health Organiza-
tion Expert Committee on Smoking Control (Technical
Report Series) Geneva 1979 World Health Organization 6
pages Price 9 Swiss francs.

Essential Hypertension Edited by Richard H. Thurm MD
Chicago 1979 Year Book Medical Publishers Inc., 41
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Louis Kuller

plete medical inventory including cardiac evaluation prior to pregnancy. To start a pregnancy and then learn later that a serious illness such as cardiac disease exists only introduces problems which could have been prevented. A satisfactory medical inventory can be obtained by a general or family physician or internist. A cardiologist may be consulted if necessary. Since any qualified cardiologist must be an equally qualified internist he can study the patient initially in close cooperation with the physician who is responsible for the obstetrics. Should illness be found which would increase the risk of pregnancy then the findings should be clearly explained and discussed with the patient and her husband. These discussions should involve the family physician and cardiologist if the cardiologist has been engaged in consideration. Most congenital heart disease advanced valvular heart disease and large hearts (especially in the presence of congestive heart failure) are contraindications for pregnancy. The patient should be the only one who can decide to have a pregnancy in spite of risks. She should then be advised that close clinical surveillance and cardiac management will be necessary throughout the pregnancy and especially near and at the time of delivery.

Patients should also be reminded that having a baby is relatively simple whereas rearing one is strenuous ever demanding and a never ending problem even for normal people. Patients with relatively mild heart disease at the time of pregnancy and delivery may have no serious difficulties during the pregnancy and during delivery but over the succeeding years the cardiac disease is most likely to worsen. Then the mother would suffer from the stresses of rearing a baby and may become incapacitated or die when the child needs a mother most. The much needed mother would leave a young offspring to suffer from the many difficulties of the world and possibly become a teenage problem or a social and economic delinquent. Planning and considerations for pregnancy must not only take into consideration the immediate period of pregnancy but the years in the future as well. These and other obvious considerations must be foremost in the physician's mind at all times. The social economic and family prognoses are the responsibilities of the family physician—the counselor of the patient, her husband and her family—as well as of all physicians concerned.

If a patient already has young children (three

others for example) it must be judiciously determined whether or not she should undertake the risk of another pregnancy possibly to be crippled for life or to die and leave behind a new baby and three young siblings and a father. Imagine what could happen to these five people left behind without the mother! Remember the whole family all people must be considered.

The physician should discuss with the family certainly with the married couple alone or with whomever else they wish the many implications, risks, advantages and potential problems that may ensue if pregnancy were to develop in the presence of the cardiac disease state. To merely recommend pregnancy and to assist the woman through pregnancy only for the mother to succumb a few years later is not a praiseworthy accomplishment.

Once pregnant the patient regardless of her state of health certainly should consult her family doctor immediately to evaluate her state of health and cardiac state in order to determine whether or not pregnancy should be allowed to continue. Also remember that none of the drugs required for the care of her heart disease may produce a congenital anomaly in the fetus. A cardiologist may be consulted if necessary when the patient is pregnant and has heart disease. These health evaluations should be made within the first 3 months of pregnancy and preferably within the first 6 weeks in the event abortion is to be seriously considered. When an abortion is considered and is carefully and thoroughly discussed with the family physician and obstetrician first and only after the medical aspects of the problem are thoroughly understood as mentioned for pregnancy evaluation then the patient and her husband should be consulted. The cardiac disease state should be properly evaluated and the decisions made as to whether or not pregnancy can or is to continue in spite of the cardiac disease. A competent cardiologist may need to be engaged to assist in the evaluation of the risks and in the management of the cardiac disease and to help the problems to be expected during pregnancy and delivery and even after delivery. When advanced heart disease is present the patient should be admitted to the hospital for the last 4 weeks of pregnancy when necessary to manage the heart disease and the pregnancy. The obstetrician decides if when and how to induce labor when induction is necessary.

When pregnant patients present themselves

To the readers of the American Heart Journal

Since 1959 I have had the pleasure of serving as Editor of the AMERICAN HEART JOURNAL. During this time the Journal has flourished and enjoyed a wide readership which is a credit to the many contributors and to the Editorial Board, the many reviewers and The C V Mosby Company, all of whom provided excellent assistance to me and to the AMERICAN HEART JOURNAL. I wish to express my thanks to all who have helped make the Journal a success. This assistance has come in a large part from readers from all over the world. The main objective of the Journal has been to help its readers, especially those dedicated to the practice of bedside and office medicine and cardiology. I hope the AMERICAN HEART JOURNAL has served this purpose effectively.

As I turn the Journal over to a new Editor, I wish him and the AMERICAN HEART JOURNAL continued success.

George E Burch MD

Editorials

Certain principles in the management of heart disease and pregnancy

G E Burch MD

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In addition to health problems due to pregnancy itself, a pregnant woman can develop any disease that a non pregnant woman can develop. However, pregnancy normally imposes changes in the cardiovascular system which usually aggravate any associated illness of the cardiovascular system and which produce extra difficulty with the outcome of the pregnancy. The normal and abnormal changes associated with pregnancy are

particularly prominent in the presence of heart disease. Heart disease is a serious illness in itself without the imposition of pregnancy to increase this seriousness. Furthermore, there are some cardiac states associated with pregnancy which actually are of little importance but which often concern the patient and her family and her obstetrician. Examples include premature heart beats. When such rhythm disturbances are present during pregnancy, the concern about them becomes even greater than usual. Therefore, there are certain general clinical medical principles which should be considered in pregnancy. Some of these principles are discussed below.

Any woman contemplating or planning a pregnancy should be examined carefully for a com-

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Thermal illness in fun running

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Almost weekly in the medical press, we read of a new complication associated with jogging—bruises blisters sprains tears penile frostbite, excoriated nipples, osteoarthritis myocardial infarction heat stroke asthma hypoglycemia amenorrhea nephropathy etc One could be forgiven for thinking that a pair of running shoes is an invitation to self destruction!

These problems multiply when the jogger is encouraged to join his compatriots for a fun run for the addition of the competitive aspect may be an ingredient responsible for the most serious of the fun runner's problems thermal injury Heat stroke is the most serious of the thermal injuries for not only can it kill but the potential number of those severely afflicted is alarmingly large It appears that fun running is still in its ascendancy and now with more than 30 million joggers on the North American continent the number of heat casualties resulting from fun runs could reach epidemic proportions

There are many reports of serious heat injuries heat exhaustion and heat stroke during fun runs in Australia Canada¹ New Zealand² and the United States³ In the United States experience probably the Peachtree Road Race in Atlanta has produced the greatest number of heat casualties One usually associates heat injury with hot humid environments however, this is not necessarily so in fun runs as the Sydney 'City to Surf' experience demonstrates Heat stroke in runners with rectal temperatures as high as 43° C have been recorded when the ambient

temperature was as low as 10° C or a comparatively effective temperature (which takes into account humidity and wind) of only 5° C

What is the predictable setting in which an injury will occur? Obviously the combination of environmental factors and the predisposed individual will be the right mix for serious injuries to occur From the 'City to Surf' experience, in the four years from 1976 to 1979 inclusive, no case of heat exhaustion or heat stroke occurred in a registered athlete who has developed the art of listening to signals of fatigue and stress from the body⁴ It is also clear that the risk of sustained heat related injuries is not the same for all runners There are large individual differences in heat tolerance and therefore predisposition to heat injury Following are some of the factors known to characterize an individual who is at greater risk

1 Insufficient acclimatization For an unacclimatized subject running in a hot environment will produce an excessively high physiological strain—higher core and skin temperatures a higher heart rate and running capacity will decline markedly This can occur classically when an athlete is transferred from a cool to a hot environment if training is done in the cooler part of the day but competition is conducted in the heat of the day or if there is an unexpected climatic change It takes about 5 to 10 running sessions in the new climate before these physiological indices return to previous levels and only then will the runner perform at his previous level the transition period athletes should reduce the intensity and duration of training runs It has been clearly shown that a disregard for these precautions will lead to undue high heat stress and predisposition to heat illness including heat stroke^{5,6}

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in pregnancy with heart disease the physician and obstetrician and the anesthesiologist consult in regard to managing the future of the pregnancy. Such problems must be individualized since no two situations are precisely the same. Close cooperation of all physicians is necessary to render adequate service to the pregnant patient.

The methods of managing a patient who is and suffering from heart disease will upon many factors. It is impossible to indicate the management in detail or even to list all of these factors. The best cardiologist and the best obstetrician are necessary for the most severe situations. The technique of delivery etc. must be left to the obstetrician and the anesthesiologist after the clinical situation has been thoroughly studied and discussed by these physicians. The general physician and/or cardiologist must begin their management of the heart disease as early as possible prior to delivery. It is a mistake to wait to start cardiac therapy or to begin anticipating problems until after they have occurred. Proper early predelivery management with proper planning prior to delivery for the time of delivery with anticipation of problems can be for a successful and happy outcome. Management continues during the puerperal period. Decisions do not end with a successful delivery. Continued management of the cardiac disease and considerations of the prevention of future pregnancies is mandatory.

With greater emphasis on pre-pregnancy exami-

nations and with routine premarital and pre-pregnancy examinations with thorough discussions the problems related to heart disease and pregnancy could be reduced to a minimum and deaths of mothers due to heart disease and pregnancy could be practically eliminated. The time to learn about the safety or hazards of pregnancy is *prior* to pregnancy. This is true not only for heart disease but for all other disease states as well. Young girls and women who have not had a thorough medical evaluation including a cardiac examination should have one prior to engaging in sexual activity with possible resultant pregnancy. Such an evaluation certainly is indicated immediately after detecting pregnancy. The decision to follow up these studies must be individualized.

When patients with heart disease are not seen until the last trimester of pregnancy or just prior to the onset of labor the family physician and/or cardiologist must work closely with the obstetrician and anesthesiologist in management with all necessary preparations, procedures and equipment being made available during delivery. The patient with heart disease regardless of how mild the problem should be continually managed by the family or primary doctor. Congestive heart failure offers the greatest difficulty. This is especially true when acute congestive heart failure develops during delivery. Shock or serious cardiac arrhythmia may further worsen the clinical problems. All of these complicated cases are most difficult to manage even by experts with considerable experience.

loads than when exercising in neutral environments " Surprising to some may be the fact that death from hypothermia may occur in fun runs when the exhausted lightly clad athlete runs in a cold windy environment "

It would therefore seem that jogging may not be safe at any time of the year But there is another side isn't there? Far from trying to stifle the present worship of physical activity, which shows no signs of being just a passing fad we too are of the faith and have also suffered some of the wounds albeit minor, of the jogging martyrdom However we do want to add a note of caution when we encourage people to be active and participate because if they are injudicious they may pay a heavy price Above all we must keep the fun in fun runs!

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2 Lack of conditioning Conditioning in a cool climate can only partially substitute for exercise in the heat as a means for acclimatization. Still the less conditioned female¹⁵ "or male"¹ runner does seem to be less heat tolerant. Less conditioned individuals also take longer to acclimatize to heat.¹⁶ Inexperienced runners may sustain heat stroke during races not necessarily due to low fitness level but rather because they select a running speed which is too fast for their ability.⁸

3 Dehydration Progressive dehydration commonly occurs during long distance running even when fluids are supplied ad libitum. Although the runner can perform well while being dehydrated, extreme fluid losses predispose one to heat stroke and acute renal failure. Of special importance is the hydration level prior to a run. Those who start exercising while dehydrated reach a higher core temperature than they would when fully hydrated prior to the exercise.¹⁷ Thus if a runner neglects to be fully hydrated before a prolonged run the risk of inadequate heat dissipation is magnified. When progressively dehydrating during prolonged exercise children and obese individuals² have a greater rise in core temperature than do lean young adults.

4 Age extremes Both young children and elderly people are more susceptible than young adults to climatic heat waves.¹⁸ During prolonged exercise in the heat children were found to have shorter tolerance time than had young adults.^{15, 17, 20} This difference is especially evident in very hot climates (dry bulb exceeding 40°C) and is attributable to greater surface area/mass ratio, lower sweating rate, greater metabolic heat production and a less efficient convection of heat from core to skin in the child. Young adolescents and children²¹ can acclimatize to heat. However children need more time than adults to reach sufficient acclimatization.² Possible causes for low heat tolerance among the exercising elderly are a lesser sweat production and a lower aerobic capacity.²²

5 Obesity Obese teenagers and adults are less heat tolerant than are lean individuals. The clinical relevance is that exercising overweight and obese people are at greater risk for heat illness including nephropathy and fatal heat stroke.^{24, 27}

6 Prior heat stroke What is the risk for a runner with a history of heat stroke to have a

relapse during subsequent running? Young adults who had sustained heat stroke during a prolonged march in hot weather were given 2 to 5 years later an exercise test in a heated climatic chamber. None of them managed to complete the task which was successfully completed by healthy controls.⁸ The reasons for incompletion were exhaustion or excessively high core temperature and heart rate. Deficient thermoregulatory capacity in people who had a history of heat stroke was also described by Robinson and co-workers.²⁸

An important question is whether such people have inherent deficiencies or whether their thermoregulatory capacity became irreversibly affected during the heat stroke episode. This question cannot be answered by the above retrospective studies. At any rate runners with a previous history of heat stroke are at a higher risk of recurrence and should be advised to avoid intense running in hot weather.

Management

Much has been written about the management of heat injuries and obviously prevention is the key particularly when one considers the large number of predisposed individuals in fun runs. These findings have been adequately reviewed elsewhere.^{1, 4, 5} In general the recommendations have fallen into three categories: (1) those related to race organization—i.e. timing of the race during the day and time of year; possible cancellation of the race if heat stress indices reach extreme levels; provision of adequate fluids; (2) competitor education—information regarding training, heat acclimatization, awareness of potential problems and likely premonitory symptoms; and (3) medical management and organization and provision of first aid stations and on site emergency treatment facilities for the rapid cooling of patients.⁸

We have concentrated on heat injury in our coverage of the thermal problems related to fun runs as these cases are obviously numerically the most important. However problems from cold or dry air arise in fun runners particularly those who may develop exercise induced asthma,²⁹ and those with ischemic heart disease who will develop angina on a cold day at lower exercise

NB Since the onset of one of these rapid cooling fatalities during the City-to-Surf race there have been no serious sequelae. The stroke in almost 100 000 competitors.

Severity of coronary artery disease in patients with diabetes mellitus. Angiographic study of 34 diabetic and 120 nondiabetic patients*

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Although the higher incidence of mortality and morbidity for cardiovascular events in patients with diabetes mellitus (DM) compared with nondiabetic patients has evidenced the role of DM as an independent risk factor for cardiovascular disease, controversies still exist about the severity of coronary artery disease (CAD) in diabetic (D) compared to nondiabetic (ND) patients. While some studies have shown an equal incidence of CAD, others have reported a higher grade of severity of CAD in D patients compared to ND patients.

Such controversies led us to re-examine our data on 34 diabetic patients who had undergone selective coronary arteriography in the last 2 years in our institution and who were found to have significant CAD and to compare their clinical hemodynamic and angiographic findings with those of a control group of 120 nondiabetic patients with CAD studied consecutively in the same period of time.

Patient population

Of the 34 patients with DM, 30 were males and four were females, with ages ranging from 39 to 68

years (mean 56 years). Patients were considered as diabetic if they were on medical treatment for DM or if they had two abnormal fasting blood sugar values. The majority of them (30 of 34) were on oral hypoglycemic agents. The group of 120 patients was composed of 120 patients, 110 males and 10 females, 37 to 67 years of age (mean 55 years).

Incidence of other coronary risk factors was similar in the two groups (Fig. 1). Smoking was indulged in by 26 diabetic patients (76%) and 89 nondiabetic subjects (74%), systemic hypertension was present in nine diabetic patients (26%) and in 28 nondiabetic subjects (23%). Hyperlipidemia was found in 11 diabetic patients (32%) and in 24 nondiabetic subjects (20%). There was a family history of CAD in eight diabetic patients (24%) and in 30 nondiabetic subjects (25%).

Fig. 2 shows the clinical findings in the groups. Of 34 patients with DM, 21 (61%) were in functional Class I to II and 12 (36%) were in functional Class III to IV of NYHA classification, while of 120 nondiabetic subjects, 80 (67%) were in Class I to II and 40 (33%) were in Class III to IV. Stable angina was the clinical presentation in 11 diabetics (35%) and in 32 nondiabetics (27%). Unstable angina was present in 13 diabetic patients (38%) and 61 nondiabetic subjects (51%). The clinical presentation was defined as one of the following: progressive angina on effort, angina at rest or intermediate effort, first onset angina, or other precursors of symptoms (atypical angina, dyspnea on exertion).

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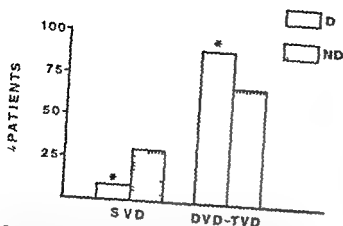


Fig 3 Incidence of multivessel disease (DVD/TV/D) and single vessel disease (SVD) in 34 diabetic (D) and 120 nondiabetic (ND) patients. $p < 0.025$ D vs ND

Table I Hemodynamic data in 34 diabetic (D) and in 127 nondiabetic (ND) patients with coronary artery disease (Mean \pm SD)

| | LVEDP (mm Hg) | CI (L/min/M) | LV dP/dT max (mm Hg/sec) |
|----|--------------------|--------------------|-----------------------------|
| D | 18.6 \pm 8 NS | 2.78 \pm 8 NS | 1.660 \pm 682 NS |
| ND | 19.0 \pm 7 | 3.07 \pm 9 | 1.855 \pm 709 |

LVEDP left ventricular end-diastolic pressure CI cardiac index LV dP/dT max maximal rate of rise of left ventricular systolic pressure

Table II Number of coronary stenoses in 34 diabetic (D) and 120 nondiabetic (ND) patients with coronary artery disease

| | Patients (No) | Stenosis (No) | Stenosis/ Patient |
|----|------------------|------------------|----------------------|
| D | 34 | 82 | 2.41 |
| ND | 120 | 251 | 2.09 |

Results

Table I shows the principal hemodynamic data for both groups. These results also include 7 diabetic patients in whom only hemodynamic data were obtained without angiographic studies. Diabetics presented a lower cardiac index and left ventricular dP/dT max, but these differences were not statistically significant.

The extent of CAD in diabetic and nondiabetic patients is shown in Fig. 3. SVD was found in three of 34 diabetic (9%) and in 36 of 120 nondiabetic patients (30%) ($p = 0.025$). Multives-

sel disease (DVD/TV/D) was present in 31 of 34 diabetic (91%) and in 84 of 120 nondiabetic patients (70%) ($p < 0.025$). Number of coronary stenoses per patient was 2.47 in diabetic and 2.09 in nondiabetic patients ($p < 0.025$) (Table II).

Fig 4 shows the distribution of CAD on major coronary arteries. Left anterior descending (LAD) was significantly involved in all 34 diabetic patients (100%) and was predominantly involved in nondiabetic patients (107 of 120, 89%). This difference between diabetics and nondiabetics had statistically significant results ($p < 0.005$). Right coronary artery (RCA) stenosis was found in 27 of 34 diabetic (79%) and in 40 of 120 nondiabetic patients (33%). Circumflex coronary artery (Cx) involvement was present in 21 of 34 diabetic (62%) and in 60 of 120 nondiabetic patients (50%). Incidence of multiple coronary artery occlusions is also shown in Fig. 4. At least one coronary occlusion was found in 15 of 34 diabetic (44%) and in 48 of 120 nondiabetic patients (40%). A total of 20 occlusions was found in the 15 diabetic patients (1.33 occlusions per patient) and a total of 55 occlusions was found in the 48 nondiabetic patients (1.15 occlusions per patient). In both groups LAD and RCA were more frequently and almost equally occluded. LAD occlusion was present in eight of 34 diabetic (23%) and in 25 of 120 nondiabetic patients (20%). Cx was occluded in four of 34 diabetic (12%) and in six of 120 nondiabetic patients (5%). Such differences were not statistically significant.

Fig 5 shows the results of left ventriculography. Eight of 32 diabetic (25%) and 60 of 115 nondiabetic patients (49%) presented with normal left ventriculography or only a localized asynergy ($p < 0.025$). No differences between diabetic and nondiabetic patients were found in the incidence of diffuse asynergy (14 of 32 diabetic, 44% vs 43 of 115 nondiabetic patients, 37%). Left ventricular aneurysm was present in 10 of 32 diabetic (31%) and in 16 of 115 nondiabetic patients (14%) ($p < 0.025$). In order to evaluate if the latter difference had to be attributed to different severity or distribution of CAD or to different development of collateral circulation, we analyzed these factors in the 10 diabetic and the 16 nondiabetic patients with LV aneurysm (Table III). No significant differences resulted in severity of CAD, incidence of occlusion of the coronary artery supplying the aneurysmatic area

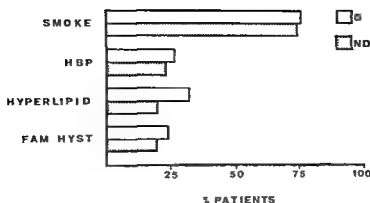


Fig 1 Incidence of risk factors for coronary artery disease in 34 diabetic (D) and 120 nondiabetic (ND) patients.

were found in two diabetic patients (6%) and in 27 nondiabetic subjects (22%). Ischemic changes on the electrocardiogram were present in 14 diabetic patients (41%) and in 65 nondiabetic subjects (54%). A history of myocardial infarction (MI) was present in 20 diabetics (59%) and in 68 nondiabetics (57%). Cardiomegaly on chest x ray was found in 18 diabetic patients (52%) and in 50 nondiabetic subjects (42%). Mean duration of symptoms was 49.2 months in diabetics and 40.8 months in nondiabetics. None of the above differences was statistically significant.

In both groups the indication for cardiac catheterization and coronary arteriography was given based on the presence of angina stable or unstable nonresponding to intensive medical management or on the presence of symptoms such as ventricular arrhythmias or atypical chest pain when it was important to exclude or confirm the clinical suspicion of CAD or finally on the presence of otherwise unexplained symptoms of left ventricular (LV) failure.

Methods of study All patients underwent cardiac catheterization, left ventriculography and elective coronary arteriography with the Sones technique.¹ Pressures were recorded with Statham P23Db transducers on an OTE photograph recorder. Cardiac output was measured by the thermodilution technique.¹ Left ventriculography was obtained by injecting 45 cc of Urografin 16% in the left ventricle at 15 cc/sec speed with a Viamonte Hobbs injector with the patient positioned in the right oblique and sometimes also in the left oblique projection. Selective coronary arteriography was also performed in multiple projections. Left ventriculography and coronary arteriography were recorded on Kodak film with

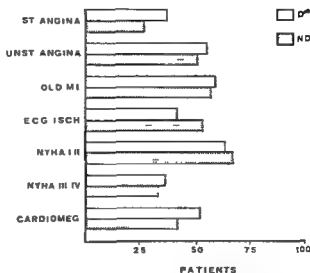


Fig 2 Clinical findings in 34 diabetic (D) and in 120 nondiabetic (ND) patients. See text for abbreviations.

the aid of a Fluoricon 300 General Electric image intensifier and a 100 mm spot camera at 6 to 8 frames/sec.

The presence and severity of segmental LV wall contraction abnormalities were graded as follows: (1) normal segmental contraction, (2) localized hypokinesia, akinesia or dyskinesia, (3) diffuse hypokinesia, akinesia or dyskinesia, and (4) LV aneurysm. On the basis of coronary arteriography, patients were subdivided in single, double and triple vessel disease (SVD, DVD, and TVD) according to the presence of significant narrowings on one, two or three major coronary arteries. A stenosis equal or greater than 50% of luminal diameter was considered as significant.

Statistical analysis was performed with the Student's *t* test and χ^2 test.

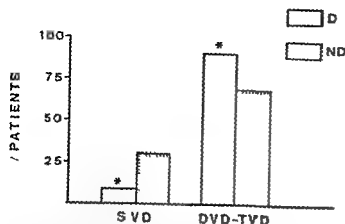


Fig 3 Incidence of multivessel disease (DVD/TVD) and single vessel disease (SVD) in 34 diabetic (D) and 120 nondiabetic (ND) patients $p < 0.02$, D vs ND

Table I Hemodynamic data in 34 diabetic (D) and in 127 nondiabetic (ND) patients with coronary artery disease (Mean \pm SD)

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LV EDP left ventricular end-diastolic pressure CI cardiac index
dP/dT max maximal rate of rise of left ventricular systolic pressure

Table II Number of coronary stenoses in 34 diabetic (D) and 120 nondiabetic (ND) patients with coronary artery disease

| | Patients (No.) | Stenosis (No.) | Stenosis/ Patient |
|----|-------------------|-------------------|----------------------|
| D | 34 | 82 | 2.41 |
| ND | 120 | 209 | 1.74 |

Results

Table I shows the principal hemodynamic data for both groups. These results also include 7 diabetic patients in whom only hemodynamic data were obtained without angiographic studies. Diabetics presented a lower cardiac index and left ventricular dP/dT max but these differences were not statistically significant.

The extent of CAD in diabetic and nondiabetic patients is shown in Fig 3. SVD was found in three of 34 diabetic (9%) and in 36 of 120 nondiabetic patients (30%) ($p = 0.025$) multives-

sel disease (DVD/TVD) was present in 31 of 34 diabetic (91%) and in 84 of 120 nondiabetic patients (70%) ($p < 0.025$). Number of coronary stenoses per patient was 2.47 in diabetic and 1.74 in nondiabetic patients ($p < 0.025$) (Table II).

Fig 4 shows the distribution of CAD on major coronary arteries. Left anterior descending (LAD) was significantly involved in all 34 diabetic patients (100%) and was predominantly involved in nondiabetic patients (102 of 120, 85%). This difference between diabetics and nondiabetics had statistically significant results ($p < 0.005$). Right coronary artery (RCA) stenosis was found in 27 of 34 diabetic (79%) and in 84 of 120 nondiabetic patients (69%). Circumflex coronary artery (Cx) involvement was present in 21 of 34 diabetic (62%) and in 66 of 120 nondiabetic patients (55%). Incidence of complete coronary artery occlusions is also shown in Fig 4. At least one coronary occlusion was found in 15 of 34 diabetic (44%) and in 48 of 120 nondiabetic patients (40%). A total of 20 occlusions was found in the 15 diabetic patients (1.33 occlusions per patient); a total of 55 occlusions was found in the 48 nondiabetic patients (1.15 occlusions per patient). In both groups LAD and RCA were more frequently and almost equally occluded. LAD occlusion was present in eight of 34 diabetic (23%) and in 25 of 120 nondiabetic patients (20%). Cx was occluded in four of 34 diabetic (12%) and in six of 120 nondiabetic patients (5%). Such differences were not statistically significant.

Fig 5 shows the results of left ventriculography. Eight of 32 diabetic (25%) and 56 of 111 nondiabetic patients (49%) presented with normal left ventriculography or only a localized asynergy ($p < 0.025$). No differences between diabetic and nondiabetic patients were found in the incidence of diffuse asynergy (14 of 32 diabetic, 44% vs 43 of 115 nondiabetic patients, 37%). Left ventricular aneurysm was present in 10 of 32 diabetic (31%) and in 16 of 115 nondiabetic patients (14%) ($p < 0.025$). In order to evaluate if the latter difference had to be attributed to the different severity or distribution of CAD or to different development of collateral circulation, we analyzed these factors in the 10 diabetic and the 16 nondiabetic patients with LV aneurysm (Table III). No significant differences resulted in severity of CAD, incidence of occlusion of the coronary artery supplying the aneurysmatic area

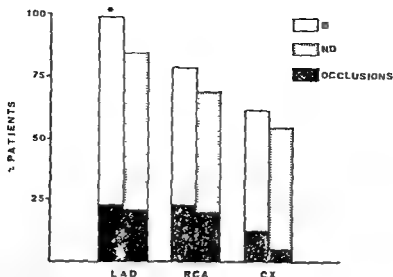


Fig 4 Frequency of significant stenoses and occlusions of major coronary arteries in 34 diabetic (D) and 120 nondiabetic (ND) patients $p < 0.005$ D vs ND

ment and extent of collateralization to the infarcted myocardial area

Discussion

Patients with and without diabetes mellitus showed similar incidence of CAD risk factors such as systemic hypertension, smoking habits and family history of CAD. Differences in age and incidence of hyperlipidemia were only minimal and were not statistically significant. Although the presence of diabetes mellitus might influence the indication to cardiac catheterization and thus preselect patients with more severe CAD, this was unlikely to be the case in our population. Over the last two years we felt that the poor angiographic quality of coronary arteries in diabetic patients which rendered them not suitable for aortocoronary bypass grafts did not justify reserving coronary arteriography only in diabetic patients with more severe angina. In fact, although in our study diabetics showed a slightly larger incidence of angina compared to nondiabetic patients (94% vs 78%), the frequency of the more severe type of angina (unstable) was practically the same (56% vs 51%) and all other clinical parameters that we analyzed were comparable. Thus we feel that diabetic and nondiabetic patients in our study can be considered as two matched groups with CAD only differing in the presence or absence of diabetes mellitus which by itself should explain the differences in the severity and distribution of CAD between the two groups.

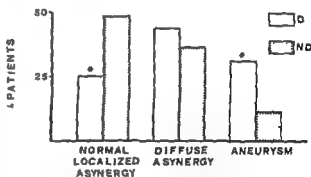


Fig 5 Findings at left ventriculography in 37 diabetic (D) and 115 nondiabetic (ND) patients $p < 0.025$ D vs ND

Other authors have compared the extent of CAD in diabetic and nondiabetic patients based upon angiographic or pathologic data. Recently, Dortumer and associates⁸ reporting coronary arteriographic findings in 37 diabetic and in 79 nondiabetic patients matched for age, sex and CAD risk factors, have described in patients with diabetes mellitus a significantly higher number of diseased coronaries per patient and a higher, although not significant, incidence of TVD compared to nondiabetic patients. Furthermore, they found no differences in the distal distribution of CAD in the incidence of bypassable vessels distal to a significant stenosis and in the frequency of collaterals to occluded coronaries. They did not comment though on differences in the degree of impairment of LV segmental contraction between the two groups. In

Combined mexiletine and amiodarone treatment of refractory recurrent ventricular tachycardia

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Refractory recurrent ventricular tachycardia represents a difficult therapeutic problem. In most cases the rhythm disorder ultimately requires the administration of a multiple drug regimen. Potentiation of the efficacy of one drug by the other is possible and satisfactory clinical results may be expected with lower doses than if each agent were given singly. This might decrease the incidence of at least some of the side effects.

The present paper is concerned with the results obtained in nine patients by using the association of a class I antiarrhythmic agent (mexiletine) with a class III agent (amiodarone).

Description of patients and methods

The study group consists of nine male patients ranging in age from 23 to 64 years (mean 53.4 years) and suffering from recurrent episodes of documented ventricular tachycardia. The first three of these cases were very critically ill individuals who had spent 10 days or more in the intensive care unit with at least five episodes of ventricular tachycardia daily (Table 1). In each instance several antiarrhythmic agents had been administered in classical dosage without any success. It is to be noted that all three patients had received intravenous mexiletine at a dose of

1 500 mg per day. This had reduced or suppressed the episodes of arrhythmia but serious gastrointestinal disorders (vomiting) had developed in all three and neurological side effects consisting of convulsions (type grand mal) had occurred in one (patient No 3). Reduction of the dose to 1 000 mg per day had allowed the rhythm disorder to recur. The remaining six cases (Table II) had a diagnosis of coronary artery disease (five patients) or congestive cardiomyopathy (one patient). They all had suffered repeated episodes of ventricular tachycardia which could not be prevented by the various drugs previously administered. These patients were referred to the laboratory of clinical electrophysiology for determination of optimum pharmacological therapy. After informed consent all cardioactive drugs were discontinued for at least 72 hours before the electrophysiological investigation by programmed electrical stimulation of the heart was conducted. The methods, apparatus and definitions used have been previously described.¹ The stimulation sequence which permitted the induction of ventricular tachycardia was characterized by using different atrial and ventricular pacing rates (up to 90/minute) and one to four ventricular premature depolarizations. Once initiation of tachycardia was achieved by pacing, the treatment by amiodarone and mexiletine was begun as indicated below. To judge the efficacy of this drug regimen, the patients were submitted to iterative electrophysiologic testing on days 3 and 7 after initiation of therapy. On each occasion the complete program of atrial and ventricular stimulation was repeated.

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Table II Patients No 4 to 9 clinical and electrophysiological data

| Case no | Age (years) | Sex | Diagnosis | ECG | Angiography | Previous treatment |
|---------|-------------|-----|---------------------------|--------------|--|--|
| 4 | 23 | M | Congestive cardiomyopathy | LAFB LVH | Left lateral ventricular aneurysm | Propranolol Digoxin Procainamide Diphenhydramine Disopyramide Amiodarone Aprindine with Quinidine Aprindine Mexiletine |
| 5 | 52 | M | Coronary artery disease | IWMI | Stenosed arteries RCA (100%) LAD (60%) 2nd diagonal (100%) segment V akinesis | Disopyramide Ajmaline Procainamide Aprindine Tocainide mexiletine Mexiletine Amiodarone |
| 6 | 54 | M | Coronary artery disease | AWMI IWMI | Stenosed arteries RCA (60%) LAD (70%) aneurysm of segments II III IV V | Mexiletine Mexaprine |
| 7 | 47 | M | Coronary artery disease | PIWMI | Stenosed arteries RCA (100%) Cx (60%) Sacciform aneurysm of segment V | Disopyramide Aprindine |
| 8 | 55 | M | Coronary artery disease | EAMI | Apical and left anterior aneurysm demonstrated by gated pool scans | Aprindine Mexaprine |
| 9 | 60 | M | Coronary artery disease | AWMI IWMI | Thrombosis of RCA and LAD aneurysm of segments III IV and V | Disopyramide Lorazepam Mexiletine |

RBBB right bundle branch block LBBB left bundle branch block RAD right axis deviation LAD left axis deviation RCA right coronary artery LAD left anterior descending artery Cx circumflex artery LAHB left anterior hemiblock LVH left ventricular hypertrophy MI myocardial infarction IW inferior wall PIW posteroinferior wall EA extensive anterior CL cycle length morphol. morphology prehospital treatment unknown

mexiletine and is totally asymptomatic (follow up 9 months) Patient No 7 received no antiarrhythmic therapy after his operation Five months later he presented a recurrence of his rhythm disorders and a control left ventricular angiogram demonstrated the reappearance of a voluminous inferior aneurysm the patient was reoperated upon and died during surgery Patients No 3 4 8 and 9 are all presently asymptomatic In one of them (patient No 3) the development of gastrointestinal discomfort at 5 weeks led to the replacement of mexiletine by another class I agent (aprindine 100 mg/day) Patient No 4 still presents on ambulatory monitoring rare bouts of ventricular tachycardia

which show a rate of 100 beats/minute and which are not perceptible to the patient

Discussion

The pharmacological treatment of recurrent life threatening ventricular tachycardia constitutes a difficult problem Most investigators agree with Zipes that it may be as naive to think that one antiarrhythmic drug will be effective for all patients as it is to think that one antibiotic will cure all infections

In this respect it seems logical to admit that at least in difficult cases the administration of an association of drugs may become necessary

Intracellular recordings on atrial and ventricular

Table 1 Clinical features of the first three cases treated by mexiletine + amiodarone

| Case no | Age (years) | Sex | Diagnosis | Arrhythmias | Previous treatment IV or oral |
|---------|-------------|------|--|-----------------------|---|
| 1 | 64 | Male | 3 attacks of myocardial infarction left and right ventricular failure | VF VT multifocal VPBs | Lidocaine Diphenhydantoin Practolol Procainamide Mexiletine digoxin Prazosin |
| 2 | 64 | Male | Hypertensive heart disease diabetes mellitus sick sinus syndrome congestive heart failure (scintigraphy posteroinferior hypofixation left ventricular enlargement) | AF VF multifocal VPBs | Xylocaine Disopyramide Practolol Mexiletine Digoxin |
| 3 | 69 | Male | 2 attacks of posteroinferior myocardial infarction residual aneurysm (aorto coronary bypass grafts on the anterior descending and circumflex arteries) | VT VPBs | Xylocaine Disopyramide Propranolol Mexiletine |

plus DC shock whenever necessary

AF atrial fibrillation VT ventricular tachycardia VF ventricular fibrillation VPB ventricular premature beats.

The treatment was given as follows. During the first two days mexiletine and amiodarone were perfused intravenously at a dose of 1 000 mg and 1 500 mg per 24 hours respectively. Simultaneously amiodarone was also given orally at a dose of 600 mg per 24 hours. From day 3 onwards the intravenous administration was interrupted and both drugs were continued orally at a dose of 600 mg daily.

Results

In the first three cases the association of amiodarone and mexiletine resulted in total suppression of the tachycardic episodes within the first three days after initiation of treatment. No electrophysiological study was performed in those patients who could be released from the intensive care unit to a normal ward after two weeks of therapy.

In the last six cases episodes of ventricular tachycardia could easily be triggered by programmed electrical stimulation. The morphology of QRS and cycle length during tachycardia are indicated in Table II. In all but one patient (No 4) the cycle length of the electrically induced tachycardia was shorter than the cycle length of the spontaneous episodes even when the QRS morphology was identical. In addition in five out of the six instances it was possible to induce during ventricular programmed stimulation

tachycardic episodes showing different QRS morphologies and cycle lengths. This pleiomorphism was associated with the existence of large aneurysmal or akinetic areas as observed at left ventricular angiography or blood pool scans. After five days of treatment no tachycardia could be elicited in patients No 6 7 8 and 9. When the six subjects were retested on day 7 none developed ventricular tachycardia.

The follow up of these patients is still rather short (Table III). Patients No 1 and 2 remained free from ventricular tachycardia but died after 2 and 5 months from intractable heart failure. One of them (patient No 2) who was known to have a sick sinus syndrome developed under the influence of treatment a severe symptomatic bradycardia which justified implantation of a pacemaker. Another patient (No 6) was lost to follow up soon after his release from hospital. He was brought dead to the emergency department 4 1/2 months later and we were not able to find out whether he had continued his treatment in the meantime. This patient had had a large anterior myocardial infarction. He had a cardiomegaly and a large aneurysmal formation. Two patients (No 5 and 7) who had suffered no relapse of tachycardia underwent cardiac surgery at 6 weeks (triple aortocoronary bypass graft—patient No 5) and 8 weeks (aneurysmectomy—patient No 7) respectively. Patient No 5 presently remains on

Table III Follow up

| Case No | Duration of follow up (months) | Description of outcome |
|---------|--------------------------------|--|
| 1 | 2 | Died from intractable heart failure |
| 2 | 5 | Died from intractable heart failure |
| 3 | 9 | At 11 weeks gastrointestinal discomfort Replacement of mexiletine by aprindine (100 mg daily) Asymptomatic |
| 4 | 5 | Asymptomatic Rare bouts of slow VT depicted at Holter monitoring |
| 5 | 11 | Triple aortocoronary bypass grafts at 8 weeks Asymptomatic |
| 6 | 4½ | Lost to follow up Sudden death |
| 7 | 8 | Aneurysmectomy at 6 weeks No antiarrhythmic therapy after operation Recurrence of VT at 7 months when administration of amiodarone and mexiletine was restarted Documented recurrence of left ventricular aneurysm Died at surgery |
| 8 | 4 | Asymptomatic |
| 9 | 6½ | Asymptomatic |
| | 56 | |

whereas no arrhythmia could be triggered in any of them after seven days of administration

The short term results obtained with the association of amiodarone with mexiletine were surely encouraging since spontaneous recurrence of the arrhythmia was prevented in all nine cases. After one week of treatment no ventricular tachycardia could be started by electrophysiologic testing in the six cases in whom tachycardic episodes had easily been initiated prior to the initiation of therapy.

The long term follow up reflects the overall rather poor prognosis of patients suffering from this type of rhythm disorder. Patient No 3 who died suddenly presented with all the markers of the highest risk group among postinfarction patients.⁴ He had had a large anterior transmural myocardial infarction. He had a cardiomegaly, an aneurysmal formation and clinical and angiographic evidence of left ventricular dysfunction of a severe degree. His demise was not unexpected and we do not even know whether he continued his treatment after his release from the hospital.

The other two subjects who died also had a guarded prognosis from the start. They had shown signs of severe right and left heart failure in the intensive care unit. In spite of the disappearance of their arrhythmia they soon died in intractable cardiac decompensation. It is impossible in these cases to rule out a deleterious influence of the antiarrhythmic treatment on cardiac function. In two patients the drug association permitted us to perform safely the invasive investigations which preceded a surgical pro-

cedure. One of these subjects is now doing well, the other died after a recurrence of his left ventricular aneurysm and simultaneously of his rhythm disorder. He was receiving no antiarrhythmic therapy at the time of his relapse. The other patients remain asymptomatic even if one of them still shows bouts of slow ventricular tachycardia on ambulatory monitoring.

In this study the efficacy of the drug cover was assessed by repeated electrophysiologic testing. Although the technique still deserves further evaluation in long term follow up studies it is thought to provide a good and fast way of selecting the drug regimen which should best protect the patients. Several recent reports suggest that the results yielded by this method correlate reasonably well with the effectiveness of long term suppressive therapy.¹¹ Although the follow up of our patients is relatively short the present observations are in agreement with this opinion.

This report admittedly lacks the strong impact of a controlled study. However all practitioners realize the difficulty of controlled studies in patients with life threatening arrhythmias. In this situation ethical problems almost always prevent the application of a rigorous scientific methodology. Nonetheless it is for this very group of patients that effective antiarrhythmic therapy is most needed. We believe that the present data provide sufficient evidence to indicate that the association of a class I with a class III agent may be of interest in the therapy of individuals with refractory recurrent ventricular tachyarrhythmias. It is apparent however that

| Spontaneous VT | | | Induced VT | | |
|----------------|------|-----------|--------------|------------|------------|
| Morphol. | Axis | CL (msec) | Morphol. | Axis | CL (msec) |
| RBBB | RAD | 220 | RBBB LBBB | RAD LAD | 370 250 |
| RBBB | RAD | 240 | RBBB | RAD | 200 |
| LBBB | LAD | 400 | RBBB LBBB | RAD LAD | 430 400 |
| RBBB | RAD | 550 | RBBB LBBB | RAD LAD | 430 400 |
| RBBB | RAD | 360 | RBBB LBBB | RAD LAD | 0 100 |
| RBBB | RAD | 240 | RBBB LBBB | RAD LAD | > 0 -30 |

antiarrhythmic effect of mexiletine can be attributed to its class I action and that this exists in spite of the shortening of action potential. In view of this one is tempted to wonder whether there might not exist a synergistic action between class I agents and substances which like amiodarone prolong the action potential duration (class III of Vaughan Williams classification). This assumption prompted us to use the association of mexiletine and amiodarone in our patients.

It should be pointed out that our work was not designed to try and demonstrate that the association of amiodarone with mexiletine is clinically superior to either drug given alone. The purpose of this paper is simply to report on the results obtained with this double drug regimen in patients with life threatening refractory ventricular tachyarrhythmias. It is worthy of note however that seven of our patients had previously received mexiletine given singly, two others had received amiodarone. The treatment had been judged unsatisfactory either because of unresponsiveness or because of the appearance of intolerable side effects.

The mode of administration was selected according to the pharmacokinetics of each of the drugs which were administered. Mexiletine is known to require a loading dose on the initiation of chronic oral therapy.⁶ This justified the parenteral administration during the first 2 days. No plasma level of mexiletine could unfortunately be obtained to demonstrate that a steady state plasma concentration within the therapeutic range was achieved. The pharmacokinetics of amiodarone are less well known and its investigation has always been hampered by the absence of a reliable method for drug plasma level determinations. It is known on a clinical basis that several days of treatment by amiodarone at 600 mg per day are required for the full antiarrhythmic efficacy to become manifest.⁷ This delay is thought to reflect the time which is necessary to build up sufficient concentrations of the drug within the myocardial cells. Amiodarone was therefore used intravenously during the first two days of treatment with the hope that this would shorten this delay and improve the reliability of drug cover. It is likely, however, that the particular characteristics of amiodarone's clinical pharmacology explains why two patients were not yet totally protected after five days of treatment.

lar muscle cells have indicated that mexiletine has according to Vaughan Williams classification a typical class I action causing a significant reduction of maximum rate of depolarization with no change of resting potential. Like lignocaine mexiletine shortens the action potential in all cardiac tissues but this effect is particularly conspicuous in that portion of the conduction system which has the longest action potential duration. As a result of this differential effect action potential duration becomes uniformly short. Some investigators have suggested that the greater uniformity of action potential duration may contribute to the antiarrhythmic action of the drug. Vaughan Williams has questioned this opinion.⁸ He believes to the contrary that the shortening of action potential might be arrhythmogenic and expresses the feeling that the

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| 8 | 4 | Asymptomatic |
| 9 | 6½ | Asymptomatic |
| | 5.8 | |

whereas no arrhythmia could be triggered in any of them after seven days of administration

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The long term follow up reflects the over all rather poor prognosis of patients suffering from this type of rhythm disorder. Patient No 3 who died suddenly presented with all the markers of the highest risk group among postinfarction patients.⁸ He had had a large anterior transmural myocardial infarction. He had a cardiomegaly, an aneurysmal formation and clinical and angiographic evidence of left ventricular dysfunction of a severe degree. His demise was not unexpected and we do not even know whether he continued his treatment after his release from the hospital.

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In this study the efficacy of the drug cover was assessed by repeated electrophysiologic testing. Although the technique still deserves further evaluation in long term follow up studies it is thought to provide a good and fast way of selecting the drug regimen which should best protect the patients. Several recent reports suggest that the results yielded by this method correlate reasonably well with the effectiveness of long term suppressive therapy. Although the follow up of our patients is relatively short, the present observations are in agreement with this opinion.

This report admittedly lacks the strong impact of a controlled study. However all practitioners realize the difficulty of controlled studies in patients with life threatening arrhythmias. In this situation ethical problems almost always prevent the application of a rigorous scientific methodology. Nonetheless it is for this very group of patients that effective antiarrhythmic therapy is most needed. We believe that the present data provide sufficient evidence to indicate that the association of a class I with a class III agent may be of interest in the therapy of individuals with refractory recurrent ventricular tachyarrhythmias. It is apparent however that

this treatment will not be able to protect patients at highest risk especially those in whom the proportion of functionally viable myocardium is so small. It may however be most helpful in less severe cases or during the period which precedes a surgical procedure consisting of coronary bypass grafting or aneurysmectomy.

Summary

A combined mexiletine and amiodarone treatment was applied in nine cases with recurrent refractory ventricular tachycardia. During the first two days of treatment mexiletine and amiodarone were perfused intravenously at a dose of 1 000 mg and 1 500 mg per 24 hours respectively. Simultaneously amiodarone was also given orally at a dose of 600 mg per 24 hours. From the third day onwards the intravenous administration was interrupted and both drugs were continued orally at a dose of 600 mg daily.

The first three patients were very critically ill and had had at least five episodes of ventricular tachycardia per 24 hours during the last 10 days in the intensive care unit. The treatment resulted in total suppression of the tachycardic episodes within three days after initiation of therapy.

In the remaining six cases ventricular tachycardia was easily initiated by programmed electrical stimulation of the heart. No arrhythmia could be elicited by repeated testing on the seventh day of treatment.

The mean follow up period was 6 months. Two patients with poor left ventricular function died in intractable heart failure. Another one died suddenly 4 ½ months after his release from the hospital. He had a large aneurysm and whether he continued his treatment is unknown. A fourth patient had an aneurysmectomy; he suffered a recurrence and died at his second operation. All the others presently remain asymptomatic.

The association of a class I (mexiletine) with a class III (amiodarone) agent is theoretically attractive for the treatment of refractory ventricular arrhythmias.

The present findings corroborate this hypothesis but show that this association is not able to protect individuals with severe underlying myocardial damage.

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Table II Hemodynamic and angiographic findings

| Electrocardiogram (QRS) | Left ventricular hypertrophy | | | Normal | | | Significance |
|--|------------------------------|----|---------|-------------|----|---------|--------------|
| | Mean | % | Percent | Mean | % | Percent | |
| Pressure (mm. Hg) | | | | | | | |
| Mean | 103 ± 20 | | | 101 ± 15 | | | NS |
| ventricular systolic | 151 ± 34 | | | 143 ± 20 | | | NS |
| ventricular diastolic | 20 ± 8 | | | 12 ± 6 | | | p < 0.05 |
| intracavitary | | | | | | | |
| End-diastolic volume (ml./m ²) | 80 ± 28 | | | 66 ± 22 | | | p < 0.01 |
| Ejection fraction | 0.52 ± 0.20 | | | 0.64 ± 0.11 | | | p < 0.01 |
| Aortic regurgitation, abnormal | | 34 | 60 | | 25 | 33 | p < 0.05 |
| Aortic regurgitation | | 14 | 25 | | 7 | 12 | NS |
| Coronary artery disease | | | | | | | |
| No vessel disease | | 9 | 16 | | 15 | 26 | NS |
| Single vessel disease | | 21 | 37 | | 24 | 42 | NS |
| Double vessel disease | | 27 | 47 | | 18 | 32 | NS |
| Main left coronary disease | | 7 | 12 | | 5 | 9 | NS |
| Left coronary artery score | 9.8 ± 2.8 | | | 9.2 ± 3.0 | | | NS |

Values given with ± 1 standard deviation.

Not significant % = number of patients.

and 30% of patients in the LVH ECG and normal QRS-ECG group respectively (100). In all instances the hypertension was considered mild with the systemic diastolic pressure ranging from 90 to 100 mm Hg. At the time of admission (Table II) there was no significant difference when the groups were compared for aortic pressures or the left ventricular pressures. Cardiomegaly was significantly (100%) more frequent in the LVH ECG (49% vs 4%).

Hemodynamic and angiographic findings in the two groups is shown in Table II. LVH ECG demonstrated evidence of greater left ventricular dysfunction as evidenced by end-diastolic pressures, end-diastolic volumes and ejection fractions. Fig 1 shows that an elevated end-diastolic pressure (> 12 mm Hg) was observed in 34% of patients in the LVH ECG group compared to 14% in the normal QRS ECG group. An abnormal end-diastolic volume (> 100 ml/m²) and ejection fraction (< 0.5) was found in 21% and 21% respectively in the LVH ECG group compared to 4% and 16% in the normal QRS ECG group. Generalized hypokinesia of the left ventricle on angiographic study was observed in six patients in the LVH ECG group while no patient in the normal QRS ECG group demonstrated this. Comparison of the severity of the coronary disease as reflected by the number of vessels involved and the frequency of main left coronary artery disease and total coronary artery

score revealed no significant differences (Table II).

LVH ECG group hypertension vs no hypertension—A comparison of the 43 hypertensive patients in the LVH ECG group with the remaining 14 nonhypertensive patients revealed 57% of the hypertensive patients to be female compared to only 8% of the nonhypertensive patients. The clinical profile of these two subgroups of patients in the LVH ECG group revealed no significant differences. The Romhilt Estes point score for left ventricular hypertrophy was similar in the hypertensive and nonhypertensive patients (6.1 ± 2.3). Mean aortic pressure was expected higher ($p < 0.05$) in the hypertensive patients (107 ± 20 mm Hg vs 90 ± 12 mm Hg). The LV end-diastolic pressures, volumes, and ejection fractions for both subgroups of patients with left ventricular hypertrophy revealed no significant differences. Generalized hypokinesia of LV contraction was observed in 77% of patients with hypertension compared to 21% without. The number of vessels involved and total coronary score for both LVH ECG subgroups revealed no significant difference; however the frequency of main left coronary artery disease was significantly ($p < 0.05$) higher in the subgroup without hypertension (29% vs. 7%).

ECG LVH group—LAE vs no LAE—Thirty patients in the LVH ECG group had atrial fibrillation; all also had cardiomegaly, abnormal end-diastolic pressures, volumes and ejection fraction.

Table 1 Clinical profile

| Electrocardiogram (QRS) | Left ventricular hypertrophy | | | Normal | | | Significance |
|----------------------------|------------------------------|-------|---------|--------------|-------|---------|--------------|
| | Mean | No | Percent | Mean | No | Percent | |
| Number of patients | | 57 | | | 57 | | |
| Male/Female | | 45/12 | | | 43/12 | | |
| Age (yrs) | 61.5 \pm 8 | | | 61.5 \pm 4 | | | |
| Duration of symptoms (yrs) | 17 \pm 11 | | | 14 \pm 9 | | | N.S. |
| Congestive heart failure | | 14 | 25 | | 0 | 0 | p < 0.005 |
| Hypertension | | 43 | 75 | | 17 | 30 | p < 0.001 |
| Diabetes mellitus | | 13 | 23 | | 8 | 16 | N.S. |
| Cigarette smokers | | 21 | 37 | | 23 | 40 | N.S. |
| Cardiomegaly | | 28 | 49 | | 2 | 4 | p < 0.005 |

Mean \pm s.e. given with \pm 1 standard deviation.

N.S. = not significant; No = number of patients; yrs. = years.

Duration of angina pectoris.

therapy accompanied by an elevated (> 120 mg dl) fasting blood sugar. Radiologic evaluation and interpretation for cardiomegaly was performed by a radiologist.

Electrocardiographic QRS voltage limits suggesting left ventricular hypertrophy were based on accepted criteria.¹ Twelve lead standard electrocardiograms taken on all patients were reviewed by at least two of the authors and a diagnosis of left ventricular hypertrophy was made on the basis of a combination of several but not necessarily all of the following electrocardiographic findings: S wave in Lead V₁ plus R wave in Leads V₄ or V₅ > 35 mm; R wave in Lead aV₁ > 11 mm; R wave in Lead I plus S wave in Lead III > 25 mm; or R wave in Lead aV₁ > 20 mm; ST-T segment and T wave deflection (with or without digitalis) in a direction opposite to the main QRS was noted. Left atrial enlargement (LAE) was diagnosed if the terminal negativity of the P wave in Lead V was 1 mm or more in depth, accompanied by a duration of 40 msec or more.

The Romhilt-Estes point score system for ECG diagnosis of left ventricular hypertrophy was also utilized.¹ The ECG in the 57 control patients (normal QRS ECG group) were in all instances reviewed by two readers who agreed that the QRS was normal.

The various methods utilized to evaluate patients in this study have been previously described in detail.¹ Essentially all patients underwent right and left heart catheterization as well as left ventricular and selective coronary angiography. Left ventricular angiograms were performed to evaluate wall motion and to deter-

mine end diastolic volumes and ejection fractions. The left ventricular contractile pattern was determined by superimposing the end-diastolic and end-systolic silhouette of the left ventricular angiogram utilizing criteria previously described. Selective coronary arteriograms were reviewed to determine the number of major arteries (left anterior descending, circumflex and right coronary artery) involved with significant disease—i.e. narrowing of an artery by more than 50% of the wall lumen. The severity of involvement of each of the major coronary arteries was graded on the basis of a score from 0 to 6 as defined by Bruschke.⁴ The total coronary score was the sum of the scores of the three major coronary arteries. Involvement of the main left coronary artery was considered separately. All information was tabulated and evaluated by standard statistical methods.

Results

LVH ECG group vs normal QRS ECG group
The clinical profile of patients meeting electrocardiographic criteria for left ventricular hypertrophy (LVH ECG group) is shown in Table 1 and is compared with 57 patients matched for both age and sex but having a normal QRS complex (normal QRS ECG group). The duration of symptoms in these two groups of patients were not significantly different and in all instances the patients were evaluated because of angina pectoris. However 25% of the patients in the LVH ECG group had a history of congestive heart failure compared to none in the normal QRS ECG group (p < 0.005). Hypertension was noted

Table III Hemodynamic and angiographic findings as related to atrial enlargement

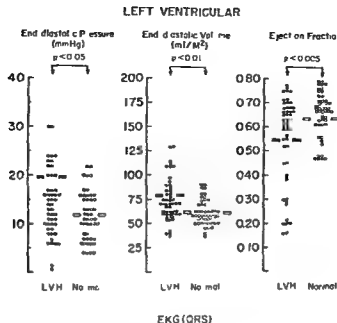
| | Left atrial enlargement | | | No left atrial enlargement | | | Significance |
|---|-------------------------|----|---------|----------------------------|----|---------|--------------|
| | Mean | No | Percent | Mean | No | Percent | |
| Number of patients | | 30 | | | 21 | | |
| Left ventricular | | | | | | | |
| End diastolic pressure (mm Hg) | 16 \pm 9 | | | 13 \pm 5 | | | NS |
| End-diastolic volume (ml/m ²) | 83 \pm 31 | | | 70 \pm 17 | | | NS |
| Ejection fraction | 0.50 \pm 0.18 | | | 0.64 \pm 0.17 | | | p < 0.01 |
| Abnormal (<0.5) | | 13 | 43 | | 3 | 13 | p < 0.01 |
| Contractile pattern abnormal | | 22 | 73 | | 9 | 3 | p < 0.01 |
| Coronary artery disease | | | | | | | |
| Single vessel disease | | 1 | 3 | | 7 | 29 | p < 0.01 |
| Double vessel disease | | 16 | 53 | | 4 | 17 | p < 0.01 |
| Triple vessel disease | | 13 | 43 | | 13 | 4 | NS |
| Main left coronary disease | | 2 | 7 | | 4 | 17 | NS |
| Total coronary artery score | 10 \pm 3 | | | 9 \pm 3 | | | |

LVH) without evidence of a prior transmural myocardial infarction or intraventricular conduction disturbance. These patients represent only 3.9% of our population of patients with ischemic heart disease seen during a four year period. Conclusions based on this study are thus limited by the patient referral and the criteria for selection into the study.

This study was motivated by the prospective epidemiological work ofannel and associates¹¹ and Chung and co workers. In the Framingham study, a threefold increased risk of developing coronary artery disease was noted in the presence of ECG LVH even after adjustment for the effect of coexisting hypertension. ECG LVH was associated with an increased risk of all clinical manifestations of coronary artery disease and in particular with a coronary death. In 40% with ECG LVH death occurred at the initial coronary event. Combining the experience from both Framingham and Albany¹² indicated that ECG LVH and the presence of another coronary risk factor strongly suggested the presence of occult coronary artery disease. Men with ECG LVH had a fivefold increase in risk of sudden death¹³ and 29% presented with sudden death compared to 10% among those without this electrocardiographic abnormality. Thus the Framingham study suggested that ECG LVH was a marker of latent coronary artery disease and was associated with an ominous prognosis. In the Tecumseh Study¹⁰ the six year incidence of sudden death (per 1000 population) in those with ECG LVH was 48, compared to 21 in those with a normal electrocardiogram and almost comparable to sub-

jects demonstrating ventricular premature beats (61 of 1000 population). In a study by Dison and associates¹⁴ ECG LVH in patients having coronary artery disease was associated with a significant (p < 0.005) linear correlation for a cardiac death.

The present study demonstrates both clinical and hemodynamic findings of significant left ventricular dysfunction in a large number of patients with ECG LVH. This was readily evident in comparison to age sex matched controls also referred because of symptomatic coronary artery disease but without ECG LVH. In both groups of patients (ECG LVH and ECG normal QRS) there was no significant difference in the duration of symptoms and no patient had a clinical history of electrocardiographic evidence of a prior myocardial infarction. The difference in left ventricular function (Fig 1) between the two groups of patients could not be explained on the basis of the severity of the coronary artery disease (Table I). Hypertension was expected to be present in three quarters of the patients with ECG LVH and no doubt contributed to the findings in the present study. The combination of hypertension and ECG LVH was present in 41 patients. In our experience¹⁵ 30% of patients evaluated with coronary artery disease have documented hypertension. Thus of the 41 patient population reviewed 13 had ECG LVH but only 10% had hypertension. Hypertension in combination with coronary artery disease could well explain the high incidence of left ventricular dysfunction observed in the present study in the ECG LVH group. It



EKG (QRS)

Fig 1 Parameter of left ventricular function evaluated in study patients. Each point represents the value of an individual patient with the horizontal bar being the mean for each group.

Of the remaining 54 patients in normal sinus rhythm 24 had normal P wave contours while 30 had left atrial enlargement by ECG. Evaluating these two subgroups (left atrial enlargement present or absent) with left ventricular hypertrophy revealed no significant difference in their clinical profile except for a greater frequency ($p < 0.05$) of cardiomegaly in the subgroup with left atrial enlargement (59% vs 29%). The left ventricular hemodynamics and angiographic findings in these two subgroups with left ventricular hypertrophy are shown in Table III. Of note is the significantly ($p < 0.01$) lower ejection fraction in the subgroup with left atrial enlargement. An abnormal ejection fraction (< 0.5) was present in 43% with left atrial enlargement by ECG compared to 13% with normal P waves ($p < 0.025$). Furthermore 73% of patients with such atrial enlargement had an abnormal left ventricular contractile pattern compared to 38% without atrial enlargement ($p < 0.01$). Single vessel coronary disease was more frequent (29% vs 3%) in the subgroup without atrial enlargement ($p < 0.01$). The frequency of main left coronary artery disease was 7% and 17% respectively in those with and without left atrial enlargement.

ECG LVH group—ST T wave changes vs normal ST T wave. Finally an evaluation of the LVH ECG group on the basis of ST segment and T wave changes revealed that of the 44 patients

with such changes 57% had cardiomegaly compared to 23% in those without ST and T wave abnormalities ($p < 0.005$). Congestive heart failure was also more frequent (30% vs 8%) in those with ST segment and T wave changes. Left ventricular hemodynamics revealed no significant differences when evaluated on the basis of the presence or absence of ST segment and T wave. Generalized hypokinesia was present in six patients with ST and T wave abnormalities. In all of these the left ventricular end diastolic pressures, volumes and ejection fractions were abnormal. The severity of the coronary artery disease revealed no significant differences when those with ST segment and T wave abnormalities were compared to those with normal ST and T waves.

No relationship was observed between the Romhilt-Estes point score of left ventricular hypertrophy and any parameter of left ventricular function—i.e., end-diastolic pressure, volume, ejection fraction or contractile pattern. Similarly the severity of coronary artery disease could not be related to the LVH point score.

Discussion

The present report reviewed a select subset of patients referred because of angina pectoris not readily controlled by medical management. The criteria for selection was documented coronary artery disease and an electrocardiogram demonstrating left ventricular hypertrophy (ECG

left ventricular dysfunction (Table III). Prior studies by Rios and co workers¹⁻³ demonstrated that left atrial enlargement in patients with coronary artery disease is correlated with left ventricular dysfunction. Thus, left atrial enlargement in patients with coronary artery disease was associated with a higher left ventricular end-diastolic pressure and increased frequency of left ventricular contractile abnormalities. Further it was observed^{1,3} that left atrial enlargement was also associated with increased severity of coronary artery disease, a finding not confirmed in our patient population with ECG LVH. All three patients with ECG LVH combined with atrial fibrillation had severe left ventricular dysfunction. Evaluating ECG LVH further on the basis of abnormal ST segments and T waves was not found helpful in identifying a subgroup with either left ventricular dysfunction or more severe coronary artery disease.

From the observations it is concluded that ECG LVH in patients with ischemic heart disease defines a group of patients with an increased frequency of left ventricular dysfunction especially if ECG left atrial enlargement is also present. This finding cannot be explained on the basis of prior myocardial infarction. No patients had a clinical history or electrocardiographic evidence of such infarction. The presence of myocardial hypertrophy and coronary artery disease would certainly bring on a disparity between oxygen demand and supply which, if protracted, could result in ischemic myocardial fibrosis. The stimulus for myocardial hypertrophy be it hypertension or chronic ischemia results in increased muscle mass receiving a limited oxygen supply. The subgroup of patients with ECG LVH and no prior history of hypertension presented with an excess frequency of main left coronary artery disease. On the basis of these findings as well as prior clinical observation it certainly appears warranted that patients with ECG LVH and suspected coronary artery disease should undergo full evaluation in order to define the coronary anatomy and left ventricular function.

Summary

The present investigation defines left ventricular function and coronary artery anatomy in a group of patients with electrocardiographic evidence of left ventricular hypertrophy (ECG LVH) and documented coronary artery disease.

The ECG LVH group consisted of 57 patients who were matched with age/sex controls. All patients were evaluated because of angina pectoris and no patient had a history or ECG evidence of prior myocardial infarction. The duration of symptoms in both groups was not significantly different. Hypertension (75% vs 30%), congestive heart failure (25% vs 0%) and cardiomegaly (4% vs 4%) were significantly more frequent in the ECG LVH group. The ECG LVH group demonstrated greater left ventricular dysfunction evident in a higher left ventricular end-diastolic pressures (20 ± 8 vs 12 ± 9 mm Hg) and diastolic volumes (80 ± 28 vs 66 ± 27 ml/m²) and lower ejection fractions (0.55 ± 0.20 vs 0.64 ± 0.17). The severity of the coronary artery disease as reflected by the number of vessels involved and total coronary score revealed significant group differences. The ECG LVH group was further divided based on ECG left atrial enlargement (LAE). Such evidence of LAE was associated with a higher frequency of congestive heart failure (59% vs 29%) and a significant ($p < 0.01$) lower ejection fraction (0.50 ± 0.20 vs 0.64 ± 0.17), as well as higher frequency of an abnormal contractile pattern (76% vs 37%). Evaluation of the ECG LVH group with the Romhilt-Estes point score for the ECG or the presence of abnormal ST segments and T waves revealed no significant difference in left ventricular function. Patients with hypertension compared to those with no hypertension revealed no differences in LVH point score or left ventricular function; however, main left coronary artery disease was significantly ($p < 0.05$) more frequent in the ECG LVH subgroup with no hypertension (29% vs 7%).

It is concluded that ECG LVH in patients with coronary artery disease defines a group of patients with increased frequency of left ventricular dysfunction especially when associated with LAE. Furthermore such ECG findings in the presence of ischemic heart disease defines a subgroup of patients with an excessive frequency of main left coronary artery disease. These observations may in part explain the poor prognosis previously described from epidemiological studies of patients with ECG LVH and coronary artery disease.

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ever in a review of our data it was observed that hypertensive patients in our control (normal QRS) group were not characterized by left ventricular dysfunction. Thus the finding of LVH on the electrocardiogram in a patient with ischemic heart disease suggests that such a finding may be a marker for left ventricular dysfunction.

Romhilt and Estes¹⁴ observed on the basis of a point score system that 62.2% of autopsied hypertrophied hearts met enough electrocardiographic criteria for left ventricular hypertrophy to achieve five points. Such criteria were more sensitive from patients with both hypertension and coronary artery disease such a combination was associated with an 88.2% sensitivity compared to 45% with only hypertension and 54.4% with only coronary artery disease. A comparison of the point score in our patients with ECG LVH in those with an without hypertension revealed no significant differences. Utilizing a point score of 5 or more there were only 3.3% false positive.

Why 25% of our patients without hypertension had ECG LVH is uncertain. It is possible that some of these patients had clinically unrecognized myocardial infarction and prior undiagnosed hypertension. It is well appreciated that in some patients preexisting hypertension may not persist after a myocardial infarction.^{15,16} It is also possible that the ECG LVH observed in some of our patients represents a conduction disturbance rather than true myocardial hypertrophy. Such a hypothesis is based on the investigations of Piccolo and associates¹⁷ who observed that ECG LVH in some patients was dependent on slowed conduction in the left bundle branch system suggesting that the anatomical hypertrophy may play a less important role. Such a mechanism for ECG LVH may well explain the low sensitivity of the electrocardiogram in diagnosing anatomic left ventricular hypertrophy.¹⁸ Finally it is well recognized that coronary atherosclerosis per se may be associated with cardiac hypertrophy.¹⁹ Pathologic studies^{20,21} have repeatedly demonstrated that myocardial hypertrophy is frequently found with coronary artery disease especially in the setting of preexisting hypertension and congestive heart failure. In the pathologic study of Ellis and co-workers²² who excluded cases with hypertension it was observed that cardiomegaly can occur in coronary artery disease even in the absence of congestive heart failure. Cardiac hypertrophy was present in 43% of patients with prior myocardial infarction and no history of

congestive heart failure. In 17% of their cases cardiac hypertrophy was observed even in the absence of a prior myocardial infarction or congestive heart failure indicating as suggested by Mallory and co-workers that coronary atherosclerosis by itself may stimulate cardiac hypertrophy. Experimental studies in the rat reported by Norman and Coers have demonstrated that ligation of the left descending artery can result in hypertrophy of the left ventricle after 12 weeks. Quantitative angiocardigraphic studies have demonstrated that ischemic heart disease is commonly associated with increased left ventricular mass. Furthermore such studies suggest that the increased left ventricular mass is related to the severity of the coronary artery disease. In our study group 47% of patients with ECG LVH had triple vessel disease compared to 32% in the age sex matched controls. Pech and co-workers²³ speculated that the reparative process after hypoxic necrosis may result in compensatory hypertrophy of the remaining myocardium.

Whether or not such changes in the left ventricular myocardium as discussed above can explain ECG LVH in patients with coronary artery disease and no preexisting hypertension is only speculative. Interestingly those patients with ECG LVH and no hypertension had a similar Romhilt Estes point score for ECG LVH when compared to patients with hypertension. Furthermore a comparison of left ventricular function in these two ECG LVH subgroups revealed no significant differences in the parameters evaluated. However the most striking finding was the higher frequency ($p < 0.05$) of main left coronary artery disease in the nonhypertensive ECG LVH group (29%) as compared to the hypertensive ECG LVH group (7%). In a prior report by Cohen and Gorlin²⁴ the frequency of ECG LVH in patients with main left coronary disease was observed to be 9.6% which is more than twice the frequency (3.9%) we have noted in over 1000 selected patients with documented ischemic heart disease. Furthermore long term follow up of patients with main left coronary artery disease indicated that ECG LVH adversely affects the prognosis.²⁵ It is tempting to speculate that the ominous prognosis associated with ECG LVH may in part be related to the excessive high frequency of main left coronary artery disease observed in this nonhypertensive ECG LVH subgroup.

Combining ECG LVH and the presence of left atrial enlargement further defines patients with

Comparison of the inotropic action of digitalis and isoproterenol in younger and older individuals

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Digitalis and isoproterenol both increase myocardial contractility and are used clinically for the support of the failing myocardium

There has been much discussion about the use of digitalis in the elderly. It is well known that older individuals even when they do not present with any definite abnormalities differ functionally from their younger peers.¹ Specifically renal function and creatinine clearance deteriorate with age. This together with a decrease in muscular mass account for prolongation of digoxin half life and diminution of the volume of distribution which renders older individuals susceptible to digoxin overdosage. In many studies,² increased incidence of digitalis intoxication has been observed in the elderly. This however has not been substantiated in more recent prospective studies. Some clinicians have discontinued digitalis in elderly persons without documenting any difference in their cardiovascular status. Similarly Starr and Luchs³ could not discern any positive inotropic effect of digitoxin in elderly women using the force ballistocardiogram. It is interesting however that no actual clinical study exists in which the inotropic action of digitalis has been compared in younger and older individuals.

We undertook to study the action of digitalis in persons younger and older than 60 years of age

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by the use of systolic time intervals. This technique has been employed quite often for the evaluation of the action of digitalis on the myocardium.⁴ We also employed the same technique to assess the inotropic action of isoproterenol on the cardiac function of older people. In a recent study Lakatta and associates⁵ found that the myocardium of aged laboratory animals is less sensitive to catecholamines than that of younger ones.

Patients and methods

1 Digitalis study Two groups of individuals were compared in Group A 10 were male and 9 were female. Ages ranged from 15 to 55 years (mean 34.3). In group B (15 males and 15 females) ages ranged from 60 to 76 years (mean 67.3). All individuals in both groups were judged to be free of overt heart disease by clinical, electrocardiographic and radiologic evaluation.

In both groups the following systolic time intervals (STI) were measured in the basal rest and supine position between 800 to 1000 A.M.—electromechanical systole (QS), left ventricular ejection time (LVET) and pre-ejection period (PEP), the heart rate (HR), corrected indices of these intervals (QS, LVET, PEP) were also estimated. The PEP/LVET and PEP/LVET ratios were also calculated. The PEP/LVET ratio was also corrected for HR according to the regression equations formed by our group and was termed the c(PEP/LVET) ratio. According to these equations c(PEP/LVET) = PEP/LVET + 0.00168 HR.

After the initial study 12 mg. digoxin was given

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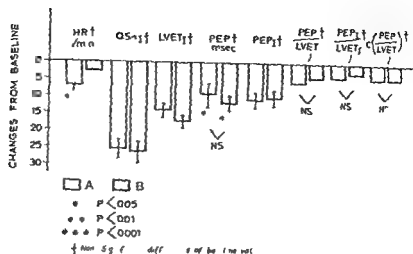


Fig 1 Changes in systolic time intervals after the administration of deslanoside C 1.2 mg intravenously. Group A (Group B) Changes from the baseline are expressed in the ordinate

Table II Influence of isoproterenol infusion (2 µg/minute × 5 minutes) on systolic time interval

| | HR/ min | QS (msec) | QS ₁ | LVET (msec) | LVET ₁ | PEP (msec) | PEP ₁ | PEP/ LVET | PEP/ LVET ₁ | CPEP/ LVET |
|------------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|------------------------------|------------------------------|----------------------------|------------------|---------------------------|----------------|
| 1 Before isoproterenol | | | | | | | | | | |
| Group A | 83.7 ± 2.7 | 370.2 ± 8.8 | 530.5 ± 5.7 | 267.4 ± 6.2 | 402.3 ± 5.1 | 102.8 ± 5.8 | 136.1 ± 5.2 | 0.386 ± 0.013 | 0.339 ± 0.013 | 0.48 ± 0.05 |
| Group B | 63.8 ± 2.9 | 399.1 ± 4.3 | 535.7 ± 3.6 | 301.5 ± 5.8 | 412.8 ± 3.9 | 102.3 ± 3.1 | 123.5 ± 3.9 | 0.337 ± 0.014 | 0.299 ± 0.010 | 0.4 ± 0.1 |
| Difference between A and B | -17.5 p < 0.001 | +27.9 | -3.8 | +34.1 | +9.9 | -0.5 | -12.6 | -0.064 | -0.040 | -0.08 |
| 2 After isoproterenol | | | | | | | | | | |
| | 118.9 ± 6.8 | 270.9 ± 10.9 | 511.5 ± 7.1 | 209.6 ± 8.3 | 407.8 ± 6.4 | 61.3 ± 4.8 | 108.9 ± 3.8 | 0.294 ± 0.014 | 0.21 ± 0.011 | 0.48 ± 0.05 |
| | 91.0 ± 2.7 | 297.9 ± 4 | 486.0 ± 7.2 | 224.9 ± 7.9 | 380.2 ± 7.1 | 68.9 ± 3.7 | 105.7 ± 4.0 | 0.312 ± 0.011 | 0.279 ± 0.012 | 0.45 ± 0.05 |
| | -27.0 | +23.0 | -25.5 | +15.3 | -22.4 | +7.6 | -3.2 | +0.018 | +0.008 | +0.02 |
| HR/ min | QS | LVET | PEP (msec) | PEP | PEP/ LVET | PEP/ LVET ₁ | PEP/ LVET | | | |
| Difference between 1 and 2 | | | | | | | | | | |
| +3.6 ± 5.7 P < 0.001 +4.7 | -29.0 ± 6.1 < 0.001 | -0.1 ± 4.3 | -41.5 ± 4.1 < 0.001 | -47.2 ± 3.9 < 0.001 | -0.099 ± 0.012 < 0.001 | -0.065 ± 0.009 < 0.001 | -0.08 ± 0.01 < 0.001 | | | |
| +2.1 ± 2.9 P < 0.001 +3.7 | -43.8 ± 3.9 < 0.001 | -32.5 ± 6.1 < 0.001 | -33.4 ± 4.5 < 0.001 | -17.8 ± 3.9 < 0.001 | -0.010 ± 0.011 < 0.001 | -0.070 ± 0.01 < 0.001 | -0.04 ± 0.01 < 0.001 | | | |
| -9.5 | -20.8 | +32.6 | +8.1 | +9.4 | +0.089 < 0.001 | +0.049 < 0.001 | +0.06 < 0.001 | | | |

HR heart rate I isoproterenol S.F.M.
Only significant difference denoted

Table 1 Influence of deslanoside C (12 mg) on systolic time intervals

| | HR/ min | QS (msec) | QS | LVET (msec) | LVET | PEP (msec) | PEP | PEP/ LVET ₁ | PEP/ LVET | c(PEP/ LVET) |
|----------------------------------|---------------|----------------|---------------|----------------|----------------|----------------|----------------|---------------------------|------------------|------------------|
| <i>1 Before deslanoside</i> | | | | | | | | | | |
| Group A | 77.6 ± 9.6 | 393.6 ± 7.3 | 55.7 ± 5.5 | 287.7 ± 5.0 | 40.7 ± 4.0 | 114.9 ± 3.9 | 145.9 ± 4.7 | 0.416 ± 0.031 | 0.359 ± 0.009 | 0.283 ± 0.015 |
| Group B | 72.5 ± 2.9 | 389.9 ± 5.6 | 54.6 ± 3.4 | 273.2 ± 5.8 | 39.9 ± 4.1 | 116.6 ± 3.4 | 145.6 ± 2.5 | 0.431 ± 0.018 | 0.369 ± 0.012 | 0.310 ± 0.017 |
| Difference between A and B | -5.1 | -3.7 | -12.1 | -14.5 | -11.8 | +1.7 | -0.3 | +0.015 | +0.010 | +0.027 |
| <i>2 After deslanoside</i> | | | | | | | | | | |
| | 70.4 ± 3.0 | 382.8 ± 7.5 | 57.2 ± 5.3 | 267.2 ± 6.7 | 39.5 ± 3.9 | 106.5 ± 7.9 | 134.7 ± 2.9 | 0.388 ± 0.012 | 0.343 ± 0.008 | 0.270 ± 0.011 |
| | 69.5 ± 9.6 | 369.5 ± 6.5 | 51.1 ± 4.2 | 262.0 ± 6.5 | 37.4 ± 10.2 | 102.8 ± 1.6 | 135.0 ± 3.1 | 0.412 ± 0.017 | 0.358 ± 0.011 | 0.297 ± 0.017 |
| | -0.9 | -13.3 | -13.1 | -14.7 | -1.1 | -3.7 | +0.3 | +0.024 | +0.015 | +0.077 |

| HR/ (min) | QS | LVET | PEP (msec) | PEP | PEP/ LVET | PEP/ LVET | c(PEP/ LVET) |
|-----------------------------------|--------|--------|---------------|--------|--------------|--------------|-----------------|
| <i>Difference between 1 and 2</i> | | | | | | | |
| -7.2 | -4.5 | -14.2 | -8.4 | -11.2 | -0.095 | -0.015 | -0.013 |
| ± 1.7 | ± 9.9 | ± 2.4 | ± 3.0 | ± 7.3 | ± 0.009 | ± 0.006 | ± 0.009 |
| <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.05 | <0.001 |
| -9.2% | | | | | -5.9% | -4.2% | -4.6% |
| -3.0 | -26.4 | -17.5 | -13.8 | -10.6 | -0.019 | -0.011 | -0.013 |
| ± 1.1 | ± 3.1 | ± 2.0 | ± 2.7 | ± 3.3 | ± 0.010 | ± 0.007 | ± 0.010 |
| <0.05 | <0.001 | <0.001 | <0.001 | <0.001 | | | |
| -4.3% | | | | | -4.4% | -3.0% | -4.9% |
| +4.2 | 0.9 | -3.3 | -5.4 | +0.6 | +0.006 | +0.004 | 0 |

HR heart rate; QS, QS; LVET, LVET; PEP, PEP; c(PEP/LVET), c(PEP/LVET).
Only significant differences are designated.

was given intravenously to all individuals and the STI were measured 60 minutes later. By this time this drug has reached a peak effect.

2 Isoproterenol study

Group A In 15 individuals (four males, 11 females) aged 22 to 42 years (mean 33.3) an intravenous infusion of 5% glucose was started 30 minutes later the STI were calculated and isoproterenol was infused at a rate of 2 µg/minute for 5 minutes. Thirty seconds after the end of the infusion STI were measured again.

Group B comprised 15 individuals (14 males, one female) aged 60 to 75 years (mean 67.7). The same procedure as in Group A was followed.

The differences in HR, QS, LVET, PEP, PEP/LVET, PEP/LVET, and c(PEP/LVET) before and after deslanoside or isoprotere-

nol were compared by the paired t test. We included PEP in both its rate corrected and uncorrected forms because in contrast to QS or LVET it does not appreciably change with HR alterations.

Results

1 Digitalis study (Table 1)

a Before administration of the drug there was no difference in heart rate or systolic time intervals between Groups A and B.

b In both groups after deslanoside a decrease in HR was observed together with shortening of the QS, LVET, PEP and PEP. The PEP/LVET, PEP/LVET, and c(PEP/LVET) ratios did not change appreciably.

The changes seen with deslanoside administra-

LVET did not significantly change. Thus our observations probably represent a real difference and correspond to the differences found in animals.¹⁴ We do not know whether any practical significance could be ascribed to this finding. However, it is possible that the therapeutic value of catecholamines is narrower in older than in younger individuals since the increases in oxygen requirements produced by these agents are not accompanied by a concomitant increase in stroke volume.

Groups A and B of the isoproterenol study were not completely comparable. Group B comprised more men than women while the opposite was true of Group A. Perhaps the difference in baseline heart frequency can be attributed not only to age which is associated with a decrease in heart rate but to sex as well: women usually manifesting higher heart rates than men. Still, if this difference in any way can be ascribed to greater sympathetic activity in Group A, this should render our results even more significant as isoproterenol would be expected to exert a smaller influence in Group A.

Summary

The positive inotropic effects of digitalis (deslanoside C 12 mg intravenously) and isoproterenol (2 µg/minute intravenously) were compared in two groups of younger and older individuals using the systolic time interval method.

Both groups responded in a completely comparable way to deslanoside C. However, after isoproterenol administration the LVET of the older group was significantly shortened. Consequently the PLP/LVET ratio did not change significantly. This difference is attributed to a lesser increase of the stroke volume in the older group.

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- (Abstract) Lewis, R P, Rutgers, S E, Forester, W F and Boudoulas, H. A critical review of the systolic time intervals. *Circulation* 56:146 (1977).

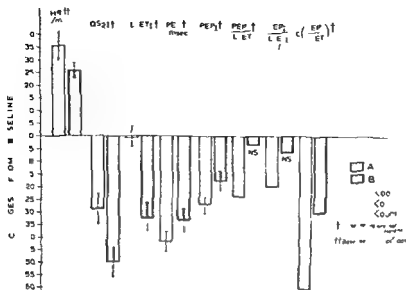


Fig 2 Changes in systolic time interval after the administration of isoproterenol, 20 μ g/minute intravenously for 5 minutes. Changes from the baseline are expressed in the ordinate.

tion were quite similar in the two groups (Fig 1).

2 Isoproterenol study (Table II)

a Before administration of the drug HR was significantly higher in Group A ($p < 0.001$) (Fig 2).

b After isoproterenol the HR increase was similar in both groups. QS, PEP and PEP, also were equally shortened. The LVET, did not change significantly in Group A but was significantly shortened in Group B ($p < 0.001$). The PEP/LVET and PEP/LVET₁ ratios decreased significantly only in Group A. The c(PEP/LVET) ratio diminished at the $p < 0.001$ level in Group A but only at the $p < 0.05$ level in Group B. Moreover the percent diminution of all three ratios was significantly greater in Group A (Fig 2).

Discussion

From our results it can be seen that digitalis exerts comparable inotropic effects on the myocardium of younger and older individuals. Our findings are similar to those of previous authors. Thus Weissler and Schoenfeld found that decreases in QS, and PEP, were more significant than LVET, Carliner and associates found significant changes of QS, PEP, PEP, and PEP/LVET with maintenance digoxin while Hoeschen and Cuddy found changes in QS and LVET

only but not in PEP or PEP/LVET. In patients with transvenous pacemakers in whom rate correction was not necessary we found a significant decrease in QS and PEP only. The conclusion of most authors is that QS, is the most sensitive index of digitalis action on systolic time intervals followed by PEP while LVET and PEP/LVET changes are variable. Thus although we did not try elegant digitalization we can say that digitalis has a definite place in the treatment of cardiac failure in the elderly. Of course provision must be made for the greater susceptibility of older individuals for toxic accumulation of the drug. We did not measure drug levels in the serum an assay difficult with deslanoside C but the dose we employed is one used quite often clinically. Our findings are at variance with those very recently reported by Guarnieri and colleagues who found that the heart of aged rats was less sensitive to ouabain than that of younger ones. However the conditions of the two studies were completely different.

We are intrigued by our results with isoproterenol. It is postulated that catecholamines affect the LVET in two diverse directions—the contraction time is abbreviated thus the LVET tends to shorten while the stroke volume is augmented tending to prolong the ejection time. We assume that in the aged individuals the stroke volume did not increase appreciably subsequently the PEP/

LVET did not significantly change. Thus our observations probably represent a real difference and correspond to the differences found in animals.¹² We do not know whether any practical significance could be ascribed to this finding. However, it is possible that the therapeutic value of catecholamines is narrower in older than in younger individuals, since the increases in oxygen requirements produced by these agents are not accompanied by a concomitant increase in stroke volume.

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The M mode echocardiogram in Fabry's disease

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Fabry's disease, an inherited glycosphingolipid storage disease, results from the defective activity of the lysosomal hydrolase, α -galactosidase A. The major glycosphingolipid substrate, trihexosyl ceramide, accumulates in plasma and the lysosomes of the kidneys, heart, and vascular endothelium.¹ The major clinical manifestations of this sex-linked disease—angiokeratoma, acroparesthesias, myocardial and cerebral infarction, and renal failure—result from progressive substrate deposition in endothelial cells and eventual occlusion of small arterioles. Deposition of trihexosyl ceramide in the myocardium and cardiac conduction system can lead to thickening of the ventricular walls and arrhythmias.² Abnormalities of the mitral and aortic valve leaflets have also been described. Findings from the physical examination, electrocardiogram, and chest roentgenogram may not indicate the full extent of cardiac involvement. The sensitive detection of such involvement may be of prognostic value in the evaluation of these patients.

Since echocardiography may provide a means

to assess noninvasively the presence and natural history of cardiac involvement in patients with Fabry's disease, a prospective echocardiographic study was undertaken in hemizygous affected males and heterozygous carrier females of this X-linked disease. Echocardiographic findings of patients with Fabry's disease have not been previously described.

Materials and methods

Thirty-two patients with Fabry's disease, 20 hemizygotes and seven heterozygotes, seen at the University of Minnesota, form the basis of this report. Each hemizygote had typical clinical findings of Fabry's disease and was shown to lack detectable levels of α -galactosidase A in plasma leukocytes and/or fibroblasts. Heterozygotes had intermediate α -galactosidase A levels and/or elevated urinary trihexosyl ceramide levels. The patients were examined for evidence of cardiac disease or hypertension.

Echocardiograms were performed with the transducer in the third or fourth intercostal space near the left sternal border and perpendicular to the chest wall while recording the mitral valve anterior leaflet. Recordings were made on a Smith-Kline Instruments ultrasonoscope interfaced with a strip chart recorder. The echocardiograms were measured with calipers where the technical quality of the recording was adequate for evaluation. End diastolic measurements were made at the time of the onset of the QRS complex. End systolic measurements were made at the time of aortic valve closure or maximal excursion of the left ventricular posterior wall. Measurements were made utilizing leading edge

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Dr. Bass was supported by the Dr. Nathan Family Fund, Minneapolis, Minn. Dr. Bass is a postdoctoral fellow from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md. Dr. Desnick is a postdoctoral fellow from the General Clinical Research Centers Program of the Division of Research Resources, Bethesda, Md.

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Reply

To the Editor

Doctors Self and Vanderbush have shown that equipment and labor inputs for the intermittent method of heparin administration may be quite a bit less than for the continuous method. This is an undeniably pertinent fact bearing on the choice of a preferred method.

Our study suggested that neither method had a clear advantage in reducing risk of serious hemorrhage. The small numbers of patients in this study limits the certainty with which this conclusion is justified. Nevertheless, until convincing evidence of less efficacy or greater risk is presented we would agree that it is quite reasonable to recommend the intermittent method on the basis of economic considerations.

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The M-mode echocardiogram in Fabry's disease

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Table 1

| Case no | Age (yrs) | Body surface area (m ²) | Diastolic IVS thickness (mm) | Diastolic LVPW thickness (mm) | IVS/LVPW ratio | IVS motion | Left ventricular dimension | | Shortening fraction | Aortic root dimension (mm) | Left ventricular diameter (mm) |
|---------------|-----------|-------------------------------------|------------------------------|-------------------------------|----------------|------------|----------------------------|---------------|---------------------|----------------------------|--------------------------------|
| | | | | | | | Systole (mm) | Diastole (mm) | | | |
| Hemizygotes | | | | | | | | | | | |
| 1 | 16 | 15 | 7 | 6 | 12 | NI | 30 | 47 | 0.36 | 30 | 28 |
| 2 | 17 | 13 | 9 | 6 | 15 | NI | 34 | 51 | 0.33 | 33 | 31 |
| 3 | 18 | 16 | 10 | 10 | 10 | NI | 32 | 45 | 0.39 | 29 | 28 |
| 4 | 18 | 13 | 10 | 7 | 14 | NI | 28 | 47 | 0.40 | 30 | 28 |
| 5 | 20 | 18 | 12 | 9 | 13 | NI | 31 | 50 | 0.38 | 33 | 31 |
| 6 | 21 | 18 | 13 | 18 | 0.7 | NI | 30 | 48 | 0.38 | 34 | 29 |
| 7 | 22 | 16 | 10 | 8 | 12 | NI | 36 | 54 | 0.33 | 31 | 30 |
| 8 | 23 | 18 | 10 | 9 | 11 | NI | 34 | 46 | 0.36 | 40 | 34 |
| 9 | 25 | 14 | 10 | 13 | 0.8 | NI | 31 | 43 | 0.28 | 38 | 29 |
| 10 | 27 | 19 | CE | CE | CE | CE | CE | CE | CE | 38 | 31 |
| 11 | 27 | 22 | 13 | 13 | 10 | NI | 33 | 50 | 0.34 | 41 | 28 |
| 12 | 28 | 23 | 12 | 9 | 13 | NI | 39 | 51 | 0.34 | 41 | 38 |
| 13 | 33 | 25 | 15 | 22 | 0.8 | NI | 54 | 72 | 0.25 | 41 | 40 |
| 14 | 34 | 20 | 17 | 13 | 13 | Flat | 31 | 47 | 0.34 | 41 | 34 |
| 15 | 30 | 20 | 15 | 12 | 1.2 | NI | 23 | 48 | 0.31 | 5 | 38 |
| 16 | 36 | 18 | 16 | 13 | 1.2 | Flat | 31 | 47 | 0.34 | 41 | 34 |
| 17 | 37 | 18 | 14 | 11 | 1.3 | Flat | 40 | 66 | 0.37 | 41 | 38 |
| 18 | 38 | 17 | 10 | 12 | 0.8 | B | CE | 47 | CE | 38 | 28 |
| 19 | 39 | 17 | 9 | 9 | 10 | NI | 29 | 51 | 0.43 | 35 | 36 |
| 20 | 39 | 18 | 15 | 14 | 1.1 | Flat | 27 | 46 | 0.41 | 40 | 32 |
| 21 | 43 | 18 | 11 | 16 | 1.1 | NI | 34 | 50 | 0.32 | 46 | 41 |
| 22 | 44 | 18 | 11 | 10 | 1.1 | B | CE | 47 | CE | 31 | 31 |
| 23 | 44 | 14 | 18 | 14 | 1.3 | Flat | 31 | 47 | 0.26 | 41 | 4 |
| 24 | 53 | 16 | 10 | 13 | 0.8 | Flat | 35 | 53 | 0.34 | 41 | 38 |
| 25 | 54 | 21 | 15 | 19 | 1.3 | NI | 23 | 40 | 0.43 | 38 | 28 |
| Heterozygotes | | | | | | | | | | | |
| 1 | 15 | 14 | 10 | 11 | 0.9 | NI | 20 | 39 | 0.36 | 30 | 28 |
| 2 | 19 | 18 | 10 | 7 | 1.4 | NI | 30 | 47 | 0.36 | 31 | 28 |
| 3 | 28 | 18 | 7 | 7 | 1.0 | NI | 30 | 41 | 0.36 | 28 | 22 |
| 4 | 41 | 16 | 11 | 9 | 1.2 | NI | 27 | 41 | 0.34 | CE | CE |
| 5 | 41 | 15 | CE | 11 | CE | CE | CE | CE | CE | 30 | 41 |
| 6 | 45 | 14 | 18 | 13 | 1.4 | Flat | 20 | 47 | 0.44 | 30 | 41 |
| 7 | 59 | 20 | 11 | 13 | 0.9 | NI | 31 | 48 | 0.35 | 31 | 3 |

Abbreviations: B = type B paradoxical intraventricular septal motion; BSA = body surface area; CE = could not evaluate; IVS = intraventricular septum; LVPW = left ventricular posterior wall; NI = normal; + = hypertensive; † = full expression in heterozygote

dimension of our 11 patients in this same age range (50.5 mm) was not statistically different. The diastolic left ventricular dimension was measured in six heterozygotes with a mean of 43.5 mm.

The left ventricular shortening fraction was calculated in 22 hemizygous patients. The nine patients under 26 years had a shortening fraction of 0.33 ± 0.05 (mean \pm standard error of the mean), not significantly different from the 13 older patients (0.33 ± 0.02 mean \pm standard error of the mean). Nor was this different from

the mean value of 0.34 found by Gertsenblith¹ associates in 37 normal adults between 20 and 44 years of age. Shortening fraction was calculated in six heterozygotes with a mean of 0.30.

The ratio of diastolic ventricular septal thickness to left ventricular posterior wall thickness was greater than 1.3 in two of the 21 normal or asymptomatic hemizygotes and in two of six heterozygotes. However, three of these four patients had a ventricular septal thickness of 10 mm or less. Only the clinically affected heterozygote had an abnormally thick ventricular septum with a ratio

present in one hemizygote who also had an apical aortic systolic murmur. Another patient with auscultatory evidence of aortic regurgitation showed aortic flutter of the mitral valve leaflets. Eccentric closure of the aortic valve was recorded in three hemizygotes who also had increased aortic root dimensions.

The aortic root dimension was measured in each hemizygote. In the nine patients less than 26 years of age the aortic root dimension was 33.2 ± 1.2 mm (mean \pm standard error of the mean) and in two (22%) it was greater than 37 mm (the maximum reported by Feigenbaum in normal adults). In the 16 hemizygotes older than 26 years the aortic root dimension was 38.1 ± 1.2 mm (mean \pm standard error of the mean; see Fig 2) and 12 (75%) showed a dimension greater than 37 mm. This difference in aortic root dimensions between the age groups was statistically significant ($p < 0.01$). Gertszenblith and associates found a mean aortic root diameter of 30.9 mm in 40 adults between 25 and 44 years of age. The mean aortic root dimension of our 15 hemizygous patients between 25 and 44 years was 38.6 mm, a statistically significant difference from normal ($p < 0.001$). When the aortic root dimension was compared to body surface area as a root function the correlation ($R = 0.34$) was not statistically significant ($p > 0.05$).

The echocardiographic aortic root dimension was measured in six of the heterozygotes and was less than 37 mm in each.

The diastolic left ventricular posterior wall thickness was measured from the echocardiograms of 21 normotensive hemizygous patients. In the patients under 26 years of age the left ventricular posterior wall thickness (9.6 ± 1.3 mm; mean \pm standard error of the mean) was not significantly different ($p > 0.05$) from the 12 patients older than 26 years (12.4 ± 0.7 mm; mean \pm standard error of the mean; see Fig 3).

Whereas two of the nine younger patients (22%) had a diastolic left ventricular posterior wall thickness greater than 11 mm (the maximum thickness reported by Feigenbaum in normal individuals), eight of the 12 older patients (67%) had a measurement greater than 11 mm. Gertszenblith and associates reported the echocardiographic diastolic left ventricular wall thickness in 33 adults between 25 and 44 years of age and found a mean of 8.7 mm. The mean thickness in our 12 normotensive hemizygotes in this same age

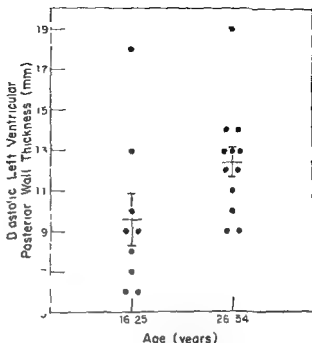


Fig 3 Distribution of echocardiographic left ventricular wall thickness in patients with Fabry's disease. Lines and intervals indicate mean \pm one standard error of the mean. The stippled area indicates the expected range of normal from Feigenbaum.

range was 11.9 mm, a statistically significant difference ($p < 0.001$). When the left ventricular posterior wall thickness was compared to body surface area as a linear function the correlation ($R = 0.42$) was not statistically significant ($p > 0.05$). The echocardiographic diastolic left ventricular posterior wall thickness was measured in each heterozygote and was greater than 11 mm in two of the seven.

Systolic and diastolic left ventricular internal dimensions were measured from the echocardiograms of 22 hemizygous patients. Of the three patients in whom these measurements were not made, two were excluded because of paradoxical ventricular septal motion and the third was excluded because the quality of the echocardiogram was technically inadequate. The diastolic left ventricular dimension in the nine patients under 26 years (47.8 ± 1.1 mm; mean \pm standard error of the mean) was not significantly different from the 13 patients over 26 years of age (50.5 ± 2.58 mm; mean \pm standard error of the mean). Gertszenblith and associates found a diastolic left ventricular dimension of 51.8 mm in 37 adults between 25 and 44 years of age. The mean

wall thickness probably reflect deposition of glycosphingolipid in the myocardium

The recent demonstration of biochemical effects of enzyme replacement in Fabry's disease increases the importance of a sensitive noninvasive technique for the assessment of effects of this therapeutic approach.⁸ Should the disease prove to be reversible, the response to this treatment could be monitored by echocardiographic evidence of regression of abnormal thickness of the left ventricular posterior wall. Changes in the aortic root dilatation would be less likely to occur. In addition the development of increasing left ventricular wall thickness or aortic root dimension while on replacement therapy would be significant. While we detected echocardiographic abnormalities in our patients we do not have sufficient serial studies to determine if echocardiography will be sensitive enough to detect changes in response to therapy.

Summary

Fabry's disease results from deficient activity of the enzyme alpha galactosidase A. Cardiac abnormalities result from glycosphingolipid deposition in the myocardium, valvular tissue and vessel walls. A noninvasive method to examine these abnormalities would be useful in the evaluation of patients. We examined the echocardiograms of 32 patients: 25 hemizygous and seven heterozygous for Fabry's disease.

The aortic root diameter was measured in each hemizygote. In nine patients under 26 years it was 33.2 ± 1.2 mm and in two it was dilated. In 16 patients over 26 years it was 38.8 ± 1.2 mm ($p < 0.01$) and in 12 it was dilated. The left ventricular posterior wall was measured in the echocardiogram of 21 normotensive hemizygotes. The difference in thickness between nine patients under 26 years (9.6 ± 1.3 mm) and 12 patients over 26 years (12.4 ± 0.7 mm) was not statistically significant. Only two of the nine younger patients had left ventricular wall thickness greater than normal compared to eight of the 12 older patients. The mean left ventricular shortening fraction of 22 hemizygous patients was normal. One hemizygote had echocardiographic evidence of mitral valve prolapse.

Four of the seven heterozygotes had normal echocardiograms. Among the other three one had increased left ventricular wall thickness, one had disproportionate ventricular septal thickness and a third had both abnormalities. The echocardiographic aortic root size was normal in all heterozygotes.

Abnormal echocardiographic findings were more common in older hemizygous patients, a distribution similar to that of the age of onset of cardiac dysfunction. Increased left ventricular wall thickness probably reflects glycosphingolipid deposition in the myocardium. Dilatation of the aortic root may result from degenerative changes of the aortic media. Abnormalities of mitral valve echoes were uncommon.

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greater than 1.3. There was no evidence of systolic anterior motion of the mitral valve or midsystolic closure of the aortic valve on the echocardiograms of any patients.

Discussion

Cardiac involvement has long been recognized in Fabry's disease.² Autopsy studies have described ballooning or interchordal hooding of mitral valve leaflets, thickening of the ventricular wall and calcification of the aortic valve leaflets.² Occasionally abnormalities of the tricuspid valve have also been noted.³ Electron microscopic studies have also shown extensive degeneration of the walls of the ascending aorta. These reports have been confined to isolated autopsy cases and the spectrum of involvement in a large group of patients with Fabry's disease has not been reported.

Echocardiography allows noninvasive evaluation of patients with Fabry's disease. Although chordae tendineae have been described as normal, the interchordal hooding in some patients with Fabry's disease³ is similar to that described in the myxomatous mitral valve.⁴ Thickening of mitral valve leaflets or a pattern of mitral valve prolapse might be detected on the echocardiogram. Thickening of ventricular walls can be easily measured by this technique. In addition, if degeneration of the ascending aorta results in dilatation, this might also be measured from the echocardiogram.

A single hemizygote had both an apical late systolic murmur and pansystolic mitral valve prolapse on the echocardiogram. Evidence of abnormalities of the mitral valve were not found on the echocardiograms of our other Fabry's patients, either heterozygotes or hemizygotes. If the abnormality of the mitral valve leaflets described in some autopsy reports in patients with Fabry's disease is common, the M mode echocardiogram did not detect it.

The aortic root dimension measured by echocardiography increased with age. There was a higher incidence of an abnormal aortic root dimension in our older patients and a statistically significant difference in the means of aortic root dimension between the two age groups.

The difference in mean left ventricular myocardial thickness between younger and older hemizygous patients was not statistically significant. However, the incidence of an abnormally thick

left ventricular wall was greater in the older patients and their wall thicknesses were greater than a comparable normal population. Left ventricular function, as estimated by the shortening fraction, was normal in our patients.

Comparison of our patients with the normal range for echocardiographic aortic root dimension and left ventricular wall thickness described by Feigenbaum seems justified, as his subjects were similar to ours in age range (13 to 54 years) and body surface area (1.3 to 2.2 M²).⁵ Aging alone cannot explain the greater aortic root dimensions and left ventricular wall thicknesses in our older hemizygous patients. When compared to age-matched subjects reported by Gertsenblith and associates,⁷ our hemizygous patients as a group had greater aortic root dimension and left ventricular wall thickness. Neither aortic root dimension nor left ventricular wall thickness correlated with body surface area, and the differences in our younger and older patients cannot be explained by differences in patient size.

We had only a small number of echocardiograms in heterozygous patients. Although one of our seven heterozygous patients was clinically affected, each had normal mitral valve echoes and normal aortic root dimensions. The left ventricular posterior wall thickness was increased on the echocardiograms of two of the heterozygous patients, only one of whom was clinically affected (this latter patient also had disproportionate ventricular septal thickening).

The M mode echocardiogram allowed us to detect abnormalities of aortic root dimension and left ventricular wall thickness in many, but not all, of our patients with Fabry's disease. Abnormal echocardiographic findings were more common in older hemizygous patients and this distribution is similar to the common onset of cardiac dysfunction in the third and fourth decade of life. The degenerative changes described by Becker and associates¹ in the aortic media may explain the increased aortic root dimensions in some patients. Dissecting aneurysms, however, have not been a problem in our patients, nor has this complication been reported by others. The absence of mitral valve abnormalities on the echocardiogram may mean that structural abnormalities in mitral valve leaflets are not common in patients with Fabry's disease or that the changes are not significant enough to be detected by echocardiography. Increases in left ventricular

Table 1 Background data on patients in the study

| Extent of disease | Number of patients | Mean age | Reason for catheterization | | | Resting ECG | | Infor- mation on ECG |
|-------------------|--------------------|----------|----------------------------|--------------------------|-------|-------------|----------|-------------------------|
| | | | Typical angina pectoris | Atypical angina pectoris | Other | Normal | Abnormal | |
| | | | | | | | | |
| 0 vessel | 13 | 48 | 6 | 6 | 1 | 10 | 3 | 0 |
| 1 vessel | 14 | 51 | 7 | 5 | 2 | 4 | 10 | 5 |
| 2 vessel | 15 | 51 | 9 | 3 | 2 | 3 | 12 | 1 |
| 3 vessel | 8 | 50 | 6 | 1 | 1 | 2 | 6 | 1 |

changes in position.^{10,12} patients were monitored at the beginning of each ambulatory ECG recording in six standardized positions (prone supine left side right side sitting and standing) ECGs were also recorded with hyperventilation and Valsalva maneuver neither of which caused any ECG changes in the group of patients studied Calibration signals were provided at the beginning of each recording by a millivolt calibrator (Del Mar Avionics Irvine Ca, Model No 456)

ECG lead system After preparation of the skin Exerstress (Del Mar Avionics Irvine, Ca) electrodes were firmly attached at the positions of CC5 (positive electrode fifth intercostal space anterior axillary line on the left negative electrode in corresponding position on the right) and modified aV_F (positive electrode below the xyphoid process negative electrode beneath the mid left clavicle) The ground electrode was positioned on the right flank The modified aV_F was found to closely resemble aV_F on scalar ECGs in 20 patients in whom both of these leads were placed and compared In this group the R/S ratio of modified aV_F was 82% of the R/S ratio in scalar aV_F Lead CC5 has been shown in the past to closely resemble Lead V₁ on scalar ECGs¹

Ambulatory ECG tapes were evaluated using a dynamic electrocardioscanner (Del Mar Avionics Irvine Ca Model No 660A) Average heart rate in each patient was determined by the total number of beats per 24 hours divided by 1440 minutes per day If any artifacts were noted during the scanning the beats counted and time elapsed during that period were excluded from analysis Random recordings each lasting six seconds were obtained at 15 minute intervals during the day (97 recordings per 24 hours) Each random recording was analyzed for ST segment deviations and considered positive if the ST segment was deviated more than 1 mm greater than any positional ST segment change noted on

baseline recordings persisting for at least 0.08 sec from the J point in at least three consecutive beats This criterion is commonly used in exercise testing¹⁴

In addition the extent of ST segment deviation on the ambulatory ECG was compared with that of simultaneously recorded scalar ECGs done during exercise testing in 23 different patients during another study ST segment deviations were noted in 0.25 mm by both methods

Times of day of all ST segment deviations were noted and were compared with entries in the patient's diaries which were completed very compulsively by the majority of study patients ST segment deviations in association with symptoms or occurring five minutes before or after symptoms were excluded from analysis and were considered separately The number of recordings with silent ST segment deviations was divided by the total number of recordings during the 24 hours to determine the percentage of observations in which silent ST segment deviations occurred Heart rate during all deviations was recorded The extent of ST segment deviations was measured independently by two observers without knowledge of angiographic findings

Angiography Coronary angiography and ventriculography were performed by using the Seldinger technique² Angiograms were analyzed in two views and were considered to reveal significant coronary artery disease if any major vessel had greater than 70% luminal diameter narrowing in one plane or greater than 50% luminal diameter narrowing in two planes Patients were then divided into groups with one two and three vessel disease Patients with normal coronary arteries and those with less than 70% luminal diameter narrowing in any major artery were considered to have zero vessel disease The results showed no difference between the subgroups of patients making up the group with zero vessel

Silent ST segment deviations and extent of coronary artery disease

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The clinical diagnosis of myocardial ischemia in ambulatory patients is usually based on a history of typical angina pectoris. However, myocardial ischemia occurs without pain and painless ST segment deviation as sometimes occurs during exercise testing may indicate the presence of asymptomatic coronary artery disease. There have been relatively few reports to delineate the prevalence of clinically silent ST segment deviations in ambulatory patients during routine activities rather than during exercise testing. The significance of such changes is as yet unknown and it is unclear to what extent they occur in apparently normal patients.

We studied 50 patients both with and without coronary artery disease as demonstrated by coronary angiography to determine the extent of silent ST segment deviations during routine daily activity. We determined the relationship of the latter to the presence and severity of coronary artery disease and to ventricular function and heart rate.

Methods

Patient population. After obtaining informed consent we studied 50 patients, all of whom had

cardiac catheterization and left ventricular angiography to evaluate typically ischemic chest pain (27 patients) or atypical chest pain (16 patients) or to evaluate coronary anatomy after myocardial infarction, syncope, episodes or episodic dyspnea (seven patients). Atypical chest pain was defined as a sticking or stabbing chest pain which was not regularly precipitated by exertion. The sample population consisted of 39 men, ages 31 to 68 and 11 women, ages 39 to 53. Patients with a left bundle branch block, valvular lesion, metabolic abnormality (abnormal calcium or potassium levels, thyroid disease) or inability to ambulate were excluded. Patients with mitral valve prolapse and those with hypertrophic cardiomyopathy were also excluded. Twenty-six patients were receiving propranolol in doses of 40 to 160 mg per day (average dose 100 mg daily). One patient was receiving propranolol in a dose of 320 mg per day and 25 patients were receiving either nitroglycerin or isosorbide dinitrate in doses of 10 to 40 mg per day at the time of the study. Five patients had received digoxin 0.25 mg per day until the day of the study.

Monitoring periods. Each patient was monitored with a two-channel ambulatory ECG (Del Mar Avionics, Irvine, Ca, Model No. 445) for 24 hours before or after cardiac catheterization. During monitoring, patients were instructed to perform their routine daily activities and to keep thorough diaries detailing stressful or unusual activities, times of meals, rest periods, and any experience of discomfort. To determine any changes in the ST segment which occurred due to

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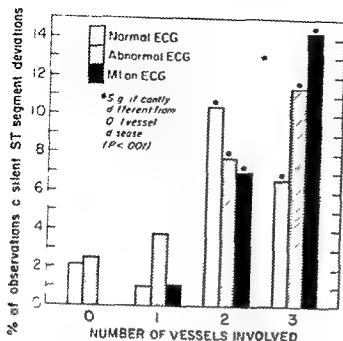


Fig 2 Effect of the resting ECG on the correlation of the prevalence of silent ST segment deviations and the extent of coronary artery disease. Clear bars represent normal resting ECGs, hatched bars represent abnormal resting ECGs, and black bars represent old myocardial infarction on the resting ECG. Silent ST segment deviations correlated with the extent of coronary artery disease regardless of the resting ECG. There was no significant difference in the prevalence of silent ST segment deviations within each class of coronary disease regardless of the resting ECG.

typical and atypical chest pain were analyzed separately and this variable did not affect results.

Silent ST segment deviations and resting ECG

Patients in each group presenting with normal and abnormal resting ECGs as well as those with old myocardial infarction on resting ECG are shown in Table I. When patients with normal and abnormal resting ECGs were analyzed separately this variable was found not to affect results (Fig 2).

Silent ST segment deviations and pharmacologic therapy. The number of patients receiving propranolol is shown in Table II. As might be expected, since more severely ill patients were more likely to receive treatment, this number increased with severity of disease. Propranolol therapy might be expected to decrease the occurrence of silent ST segment deviations. In this study, propranolol did not significantly affect the relationship between prevalence of silent ST segment deviations and the extent of coronary artery disease ($p > 0.05$) (Fig 3). Though there were numerical differences in the prevalence of silent

ST segment deviations between patients with and without propranolol within each group, this difference was not statistically significant. Patients being treated with propranolol had an average heart rate of 67 beats per minute, while those without propranolol averaged 72 beats per minute. Propranolol may never have been given to full beta blockade.

Table II also shows the percentage of patients in each disease category who were receiving nitrates. Nitrate therapy did not affect the prevalence of ST segment deviations (Fig 3). Numerical differences in the prevalence of silent ST segment deviations within each group were found in patients with and without nitrate therapy, but these differences were not statistically significant. We did not attempt to alter drug regimen of patients in our study and therefore patients were not receiving nitrates in any standard protocol.

Five patients were receiving digitalis preparations and these patients were only in the two- and three-vessel disease groups. Although digitalis may clearly influence ST segments during exercise testing, causing false positive tests, the differences in the percent of observations in 24 hours with silent ST segment deviations between groups was not influenced when patients receiving digitalis were excluded.

Silent ST segment deviations and left ventricular function. There was no relationship between silent ST segment deviations and the prevalence and degree of wall motion abnormalities. Normal or abnormal ejection fraction was also unrelated.

Silent ST segment deviation and heart rate. Increased heart rate was defined here as 10 beats per minute above the average daily heart rate. In the zero-vessel disease group, 60% of silent ST segment deviations occurred at increased heart rates and therefore may have been rate related. However, in the one-, two-, and three-vessel disease groups, only 34%, 7%, and 20%, respectively, of silent ST segment deviations occurred at heart rates higher than 10 beats per minute above the average daily heart rate. Therefore, the majority of ST segment deviations did not appear to be rate related.

ST segment deviations associated with pain. No patient with zero-vessel or one-vessel disease had any observations of ST segment deviations which were associated with pain as noted in the patient's diary. Six percent of observations of

Table II Numbers of patients displaying silent ST segment deviations and receiving medications

| Extent of disease (no of pts) | Number displaying silent ST segment deviations | Number receiving propranolol | Number receiving nitrates |
|-------------------------------|--|------------------------------|---------------------------|
| 0 vessel (13) | 5 | 3 | 6 |
| 1 vessel (14) | " | 6 | 5 |
| 2 vessel (15) | 15 | 12 | 10 |
| 3 vessel (8) | 8 | 7 | 5 |

disease. Angiographic interpretation was performed without knowledge of the results of ambulatory ECG analysis.

For evaluation of ventricular function segmental motion analysis¹⁴ of the left ventriculogram was made and the resting ejection fraction was determined. Wall motion abnormalities were expressed as being dyskinetic, akinetic and hypokinetic and the percent of the perimeter of the left ventricular silhouette with abnormal wall motion was determined.

Statistical analysis. The patients were divided into four groups: zero, one, two, and three vessel disease. The percent of silent ST segment deviation per patient was recorded and transformed using an arcsin transformation. Comparisons among the four groups were made using the analysis of variance and Duncan's multiple range procedure. All statistical tests were done using a P level of < 0.05.

Results

The number of patients in each group, their ages, reason for catheterization, and resting ECG are shown in Table I. The percentage of patients who displayed any silent ST segment deviations is shown in Table II. Thirty-eight percent of patients with nonobstructive disease and 50% of patients with one vessel involvement displayed these changes. All patients with two and three vessel disease had silent ST segment deviations.

Fig 1 shows for each group the percentage of observations in which ST segments shifted. This percentage increased with the increasing extent of coronary artery disease. The group with zero vessel disease had silent ST segment deviations an average of $2.2 \pm 1.0\%$ of observations in 24 hours; one vessel disease had silent ST segment deviations $2.9 \pm 1.8\%$ of observations in 24 hours;

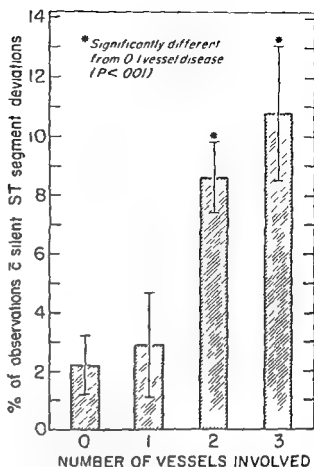


Fig 1 Correlation of silent ST segment deviations with the extent of coronary artery disease. Hatched bars represent the percentage of observations with silent ST segment deviations on the ambulatory ECG for each grade of coronary artery disease. Note how this percentage increases with the extent of coronary artery disease. See text for further discussion.

two vessel disease $8.2 \pm 1.0\%$ of observations in 24 hours; and three vessel disease $10.1 \pm 2.4\%$ of observations in 24 hours. The difference in the percent of observations with silent ST segment deviations during 24 hours between zero and one vessel disease groups when compared with the two and three vessel disease groups was significant ($p < 0.001$) while other differences were not.

The following factors had no influence on the correlation between percent of observations of silent ST segment deviations and the extent of coronary artery disease.

Silent ST segment deviations and precatheterization symptoms. Table I shows the occurrence of typical and atypical chest pain with varying extent of coronary artery disease. Patients with

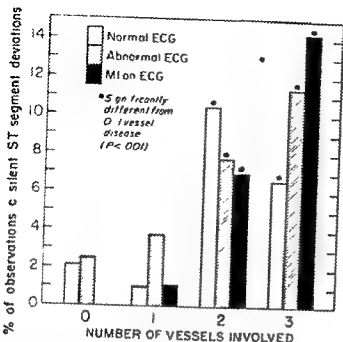


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typical and atypical chest pain were analyzed separately and this variable did not affect results.

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ST segment deviations between patients with and without propranolol within each group, the difference was not statistically significant. Patients being treated with propranolol had an average heart rate of 67 beats per minute, while those without propranolol averaged 70 beats per minute. Propranolol may never have been given to full beta blockade.

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ST segment deviations associated with pain. No patient with zero-vessel or one-vessel disease had any observations of ST segment deviations which were associated with pain as noted in the patient's diary. Six percent of observations of ST

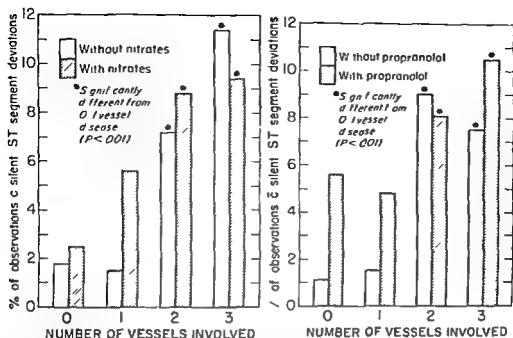


Fig 3 Lack of influence of propranolol and nitrate therapy in the doses used on the correlation of the prevalence of silent ST segment deviations with the extent of coronary artery disease. Vertical axis represents the percentage of observations in 24 hours with ST segment deviations. Hatched bars represent patients receiving medications (see text for dose). Silent ST segment deviations correlated with the extent of coronary disease regardless of propranolol or nitrate therapy in these doses. Though there were numerical differences in the prevalence of ST segment deviation between patients with and without medications within each class of disease, the differences were not statistically significant.

segment deviation in the two vessel disease group and 3% of observations in the three vessel disease group were associated with pain, and these observations were excluded from analysis.

Discussion

Clinically coronary artery disease usually presents with angina pectoris or with catastrophic events such as myocardial infarction or sudden death. Our study suggests, however, that in addition to these manifestations, there are regular and frequent dynamic electrocardiographic changes (ST segment deviations) which may reflect underlying recurrent myocardial ischemia, as has been suggested previously.^{1,2} Pain is only one of the clinically recognizable responses to ischemia, and the frequency of silent ST segment deviations suggests that painless ischemia occurs frequently in patients with obstructive coronary artery disease. Furthermore, the frequency of these ST segment deviations on the ambulatory ECG correlates with the severity of the coronary artery disease. Though no significant difference was noted between patients with nonobstructive coronary artery disease and one vessel disease or

between two and three vessel disease, there was a markedly significant difference ($p < 0.001$) between the zero and one and two and three vessel disease groups. This difference was not influenced by the patient's symptoms, resting ECG, or ventricular function, but only by the number of coronary arteries occluded. Also, since most ST segment deviations occurred at heart rates within 10 beats per minute of the average heart rate, the deviations were probably not rate related.

Previous studies of silent ST segment changes on the ambulatory ECG have been consistent with our observations in showing that they occur more commonly in patients with clinical coronary artery disease³⁻⁷ that they may have prognostic significance,⁸ and that they can occur during driving and sleep.⁹ However, comparison of silent ST segment deviations on the ambulatory ECG with the extent of angiographically proven coronary artery disease has not been previously made.

In studies using the ambulatory ECG, it is important to properly evaluate the lead system used. Ambulatory ECG systems use bipolar chest leads and differ both from conventional ECG

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most false negative exercise tests occur in patients with one vessel disease.³ Also we stress that it is not the presence of ST segment deviations but rather the total duration of ST segment deviations over 24 hours which correlates with more severe degrees of coronary disease. Ultimately though since we are unsure of the actual cause of ST segment deviations we cannot state why more silent ST segment deviations were not seen in patients with one vessel disease.

In the present study there were few episodes of ST segment deviation associated with the subjective experience of pain. The use of patient diaries has certain limitations though the importance of keeping complete records was stressed and was carried out. It is possible as well that patients voluntarily curtailed their activities because of the monitoring procedure. It must also be considered that the pharmacotherapy the patients received may have suppressed pain without altering the electrocardiographic determinants of ischemia. This may have been a function of inadequate therapy as mentioned above.

Because painless ST segment deviations on the ambulatory ECG are relatively frequent in patients with coronary artery disease, reversal of ST segment deviations may provide a more definite end point of therapy to reverse ischemia than either relief of pain or exercise testing. This technique may also be used to evaluate drug or surgical therapy.

The occurrence of frequent silent ST segment deviations in patients with two and three vessel coronary artery disease may reflect an important underlying process that is undetectable without specific and proper testing.

Summary

Fifty patients who underwent coronary and left ventricular angiography for suspected coronary artery disease (CAD) had ambulatory ECG monitoring at a time remote from that of catheterization. After correcting for positional ST segment variation on ambulatory ECG the amount of time that ST segments deviated more than 1 mm from baseline without corresponding angina was determined and these results were correlated with results of angiography. Silent ST segment deviations were seen in patients without significant CAD in 22% of observations but increased significantly with extent of coronary artery disease (29%, 82% and 101% of observations in the

one, two and three vessel disease groups respectively.) This relationship was independent of ventricular function, resting ECG and previous symptoms. It is concluded that silent ST segment deviations on ambulatory ECG reflect the presence and severity of coronary artery disease.

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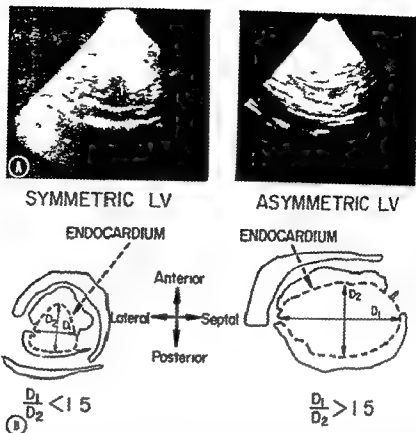


Fig 1 A Polaroid photographs of typical echocardiographic short axis images from two formalin fixed ventricles. On the left is a symmetric ventricle and on the right is an asymmetric ventricle B A diagrammatic sketch illustrates the orientation of these images. The anterior wall is above posterior wall below septal wall to the right, and lateral wall to the left. Diameters are measured as shown from septal to lateral (D_1) and from anterior to posterior (D_2). The approximate endocardial border is outlined by the broken line

sary to avoid shrinkage of the LV (left ventricular) cavity during formalin fixation and to induce either symmetry or asymmetry into the ventricular chamber. Nine left ventricles were stuffed in such a manner that the septal lateral diameter was more than 1.5 times the anterior posterior diameter. The formalin fixed left ventricles were immersed in mineral oil and were viewed with the phased array sector scanner to obtain cross sectional images (Fig 1) similar to images described in echo studies of the closed chest dogs. Six to ten short axis cross sections were obtained from base to apex by moving the transducer in the mineral oil over the left ventricle. Long axis cross-sections were obtained by rotating the transducer 90 degrees. All views were recorded on videotape and were subsequently played back for analysis. Following the echocardiographic procedures the left ventricle was removed from the mineral oil, rinsed thoroughly, and was filled from a graduated cylinder up to the mitral and aortic valve rings with a known amount of mineral oil.

This rinsing and filling procedure was performed three times and an average was obtained for the fluid volume of the left ventricular chamber. The fluid volume served as the known standard for comparison with echocardiographic determination of volume.

Determination of LV volume Using cross-sectional echocardiographic images, five mathematical models were tested by comparison of calculated left ventricular volume versus true volume. A linear regression analysis was performed on nine asymmetric ventricles and on 11 symmetric ventricles. Endocardial outlines were traced from projections of short axis and long axis cross sections during videotape stop-motion replay. As is evident from Figs. 1 and 2, echocardiographic short axis and long axis images are characterized by strong circumferential echoes at the endocardial interfaces. By tracing at the inner border of these circumferential echoes, the thickness of the endocardial echo is excluded from the endocardial area. This procedure of tracing the

Cross sectional echocardiography III Analysis of mathematic models for quantifying volume of symmetric and asymmetric left ventricles

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Previous clinical studies on left ventricular volumes¹⁻⁴ have shown that M mode echocardiography correlates well with angiography for patients with normal myocardial wall motion but not for those with regional myocardial dyssynergy. The cube method of M mode echo utilizes only one diameter measurement and is derived from the formula for the volume of a symmetrical ellipsoid. Thus inaccuracies of volume quantification should accompany any ventricular asymmetry due to regional dyssynergy.

Recently techniques were developed in this laboratory for performing noninvasive cross sectional echocardiography in closed chest dogs.⁵ With this technique a variety of left ventricular cross sectional images may be recorded for detailed analysis of cardiac size, structure, and function. This development represents a definite improvement over the one-dimensional measuring capabilities of M mode echocardiography.

Previous cross sectional echocardiographic studies from this laboratory demonstrated that left ventricular mass in the closed chest dog⁶ and left ventricular volume in the formalin fixed heart⁷ may be quantified best with mathematical models incorporating short axis area measurements. However, the adequacy of cross sectional echocardiography for quantification of left ventricular volume in the presence of substantial ventricular asymmetry has not been investigated. Thus a study of cross-sectional echocardiography was designed to investigate the influence of asymmetry on volume quantification in formalin fixed canine left ventricles. Echocardiographic cross sectional images were obtained and mathematical models were utilized similar to those for in vivo studies of the left ventricle.⁷

Methods

Cross sectional echocardiographic studies were performed with an electronic phased array sector scanner (Varian Associates, Palo Alto, CA). Features of this system include real time, high resolution, a 32 element transducer, an 84 degree sector angle, and a videotape recording rate of 30 frames per second. The 84 degree sector angle facilitates recording of entire cross sections of the left ventricle in short axis or long axis orientations.

Nineteen dogs were killed with an overdose of anesthetic and their hearts were removed. Left ventricles were separated from the rest of the heart, stuffed with gauze, and fixed in formalin for at least 3 days. Insertion of gauze was neces-

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CROSS-SECTIONAL ECHOCARDIOGRAPHY MATHEMATICAL MODELS FOR LV VOLUME

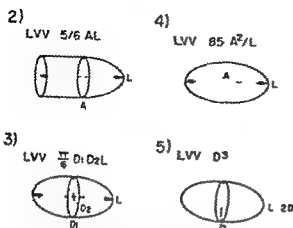


Fig 4 This figure illustrates four of the mathematic models that were utilized in this study. Each formula is accompanied by a geometric figure from which the formula was derived. Model 2 on the upper left shows that with endocardial area (A) from only one short axis cross-section and the length (L) from one long axis cross-section left ventricular volume may be calculated by the formula shown $V = 5/6 AL$, which is represented by the figure shown a half cylinder half ellipsoid. Model 3 on the lower left shows that with both minor axis diameters from one short axis section and left ventricular length (L) from a long axis section, the volume of an ellipsoid may be computed by $V = \pi/6 D_1 D_2 L$, where D_1 = septal to lateral diameter D_2 = anterior to posterior diameter. This is a standard ellipsoidal formula that has been utilized previously with cineangiography for left ventricular volume determination. With Model 4 on the upper right, the volume of an ellipsoidal figure is calculated by the standard angiographic area length formula $V = 0.85 A^2/L$, this formula utilizes both the area (A) and the length (L) from a long axis section of the left ventricle. With Model 5 on the lower right the volume of an ellipsoidal figure is calculated with the cube method formula $V = D^3$ developed specifically for M mode echocardiography. D = septal lateral diameter of the left ventricle.

Mathematical models

Model 1 (Fig 3) Length (L) was divided by the number of short axis sections to obtain an arbitrary height (h) for each short axis section. Left ventricular volume was then calculated by a short axis reconstruction procedure using Simpson's rule based upon short axis areas (A) and heights. Volume for the apical section was calculated by the formula for an ellipsoidal volume segment shown as the last two terms in the ventricular volume formula at the bottom of Fig 3. Volumes for each remaining short axis section were calculated simply by multiplying the respective area (A) of the section by height (h).

Ventricular endocardial volume (V) is obtained by summation of the section volumes,

$$V = A_1 h + A_2 h + A_3 h + \frac{A_4 h}{2} + \frac{A_5 h}{6}$$

Model 2 (Fig 4) The volume (V) of a cylinder may be simply calculated by multiplying the area (A) from a single left ventricular short axis section at the low papillary muscle level with the left ventricular length (L) determined from a long axis section. $V = AL$. The volume of the ellipsoid is calculated from the same parameters as 4 and L using the following derivation $V = 4/3 \pi r_1 r_2 r_3$ for a nonprolate ellipsoid where r_1, r_2 , and r_3 are the respective radii assuming $A = \pi r_1 r_2$ and $L = 2r_3$, $V = 2/3 AL$. Thus the only difference between the volume formulas for ellipsoid and cylinder models is a constant (2/3). Since the left ventricle may be represented by a shape that is ellipsoidal toward the apex and cylindrical toward the base (Fig 4A top left panel) the volume formula for Model 2 was approximated by averaging the constants for the ellipsoid and cylinder models $V = 5/6 AL$.

Model 3 (Fig 4) The volume of an ellipsoid is calculated from the left ventricular length (L) and both minor axis diameters determined from a short axis echocardiographic section at the low papillary muscle level. D_1 = septal to lateral diameter D_2 = anterior to posterior diameter. The formula for the volume of an ellipsoid is $V = 4/3 \pi r_1 r_2 r_3$ if $D_1 = 2r_1$, $D_2 = 2r_2$, and $L = 2r_3$, then $V = \pi/6 D_1 D_2 L$. This standard ellipsoidal formula has been utilized previously for left ventricular volume by cineangiography.

Model 4 (Fig 4) Volume of an ellipsoidal figure may be calculated by the standard angiographic area length formula utilizing the area (A) and the length (L) both from a long axis section of the ventricle. Using $V = 4/3 \pi r_1 r_2 r_3$ and assuming $r = r_1$, $r_2 = L/2$ and $A_1 = \pi r_1^2$. Then $r_1 = r_2 = 2A_1/L$, $V = 4/3 \pi (2A_1/L)^2 (L/2) = 0.85 A_1^2/L$.

Model 5 (Fig 4) Volume of an ellipsoidal figure may be calculated with the cube formula developed specifically for M mode echocardiography. This method uses the septal to lateral diameter (D) of the left ventricle measured at the low papillary muscle level. If $V = 4/3 \pi r_1 r_2 r_3$ and $r_1 = r_2 = D/2$ and r_3 is assumed = D then $V = D^3$.

Data analysis In 19 formalin fixed left ve



Fig 2 A Polaroid photograph of a typical echocardiographic long axis image of a formalin fixed left ventricle B A diagrammatic sketch illustrates the orientation of this image Above is the anterior wall below the posterior septum to the right is the base and to the left is the apex Length is measured from apex to base as indicated The approximate endocardial border is outlined by the broken line

inner echo borders was found to carry smaller interobserver variability than tracing at the center of the endocardial echo. Linear measurements were obtained from the cross-sectional outlines and areas enclosed within the outlines were obtained by planimetry. Length of ventricles was measured in the long axis section (Fig 2) as the distance from apex to the mitral ring at the base. In a previous study of two D echo in dogs left ventricular short axis diameter and area measurements in several simplified mathematic models were based on a section taken at the high papillary muscle level. Formalin fixation procedures in this study resulted in some constriction of the chamber lumen at the base of the LV so that the high papillary section was not always representative of the LV. Thus with formalin fixed left ventricles the short axis section at the low papillary muscle level two thirds of the distance between the base and apex was utilized for the simplified models.

Calibration of cross sectional echocardiograph

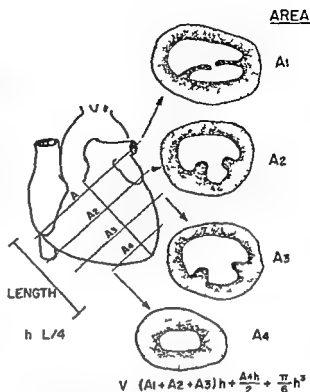


Fig 3 Sectional analysis of the left ventricle (LV) in dogs with the phased array sector scanner. Short axis cross-sectional views are obtained at four to eight levels from the base to the apex. Shown here are (1) mitral valve section (A1 = area of endocardial surface) (2) high papillary muscle section (A2 = area) (3) low papillary muscle section (A3 = area) (4) apical section (A4 = area). LV length (L) obtained from a long axis view (apex to mitral-aortic junction) is divided by the number of short axis sections to give an arbitrary height (h) for each section. Volume (V) of the chamber is calculated by Simpson's rule for summation of area height for each section except the apical section the volume of which is calculated with the formula for an ellipsoidal segment.

ic measurements was performed from scales along the horizontal and vertical axes of the images predetermined in the system used (Varian Inc) from precise fixed-distance calibrations. These calibrations were subsequently checked in our laboratory and were found to be accurate. However the calibration scale was rechecked for each echocardiographic measurement since some variation may occur with changes in gain settings and variation in calibration may also occur over the range of the screen. The calibrations were measured during videotape motion replay to allow better visualization of the scale. Calibration factors were determined and were applied to each volume calculation.

CROSS SECTIONAL ECHO

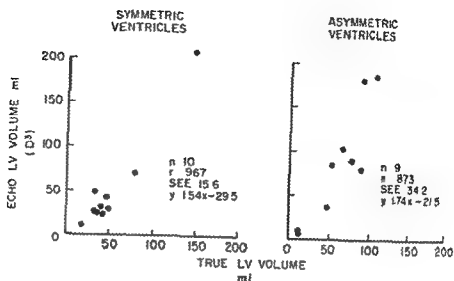


Fig 6 Comparison of volume in formalin fixed left ventricle cross sectional echocardiography (cube method, Model 5) on the Y axis versus true volume on the X axis. A linear regression analysis was performed for calculated versus true volume. The regression equation is shown. The correlation coefficient was excellent for symmetric ventricles ($n = 10$) but substantially lower for asymmetric ($n = 9$) ventricles: 0.967 and 0.873 respectively. N = number of ventricles; r = correlation coefficient; SEE = standard error of estimate.

Table 1 Summarized results of linear regression and percent error analyses for echocardiographic volume versus true volume utilizing 5 mathematic models

| | REC | S/B AL | $\pi/6 DD_L$ | 0.85 A/L | D |
|-------------------------|---------------|----------------|----------------|----------------|-----------------|
| 10 symmetric ventricles | | | | | |
| Model | 1 | 2 | 3 | 4 | 5 |
| r | 0.996 | 0.993 | 0.984 | 0.972 | 0.967 |
| M | 0.98 | 1.34 | 0.98 | 0.81 | 1.54 |
| I | +0.91 | -12.0 | -10.88 | +0.03 | -29.46 |
| SEE | 3.37 | 6.13 | 6.81 | 7.52 | 15.65 |
| MPE | 5.9 \pm 1.2 | 10.1 \pm 3.0 | 26.6 \pm 3.1 | 30.9 \pm 4.8 | 29.8 \pm 4.1 |
| 9 asymmetric ventricles | | | | | |
| Model | 1 | 2 | 3 | 4 | 5 |
| r | 0.985 | 0.974 | 0.956 | 0.886 | 0.873 |
| M | 0.95 | 1.11 | 0.69 | 0.48 | 1.71 |
| I | +0.57 | -9.04 | -0.97 | +2.19 | -21.48 |
| SEE | 6.83 | 9.09 | 7.53 | 8.93 | 36.77 |
| MPE | 9.8 \pm 2.8 | 20.3 \pm 9.0 | 25.4 \pm 5.0 | 52.1 \pm 3.0 | 53.5 \pm 13.1 |

REC = reconstruct on using Simpson's rule; r = correlation coefficient; M = slope; I = intercept; SEE = standard error of estimate; MPE = mean percent error.

significantly from corresponding values for Model 1. With Model 3 (Table 1) the short axis diameter length method correlation coefficients were also excellent for both symmetric and asymmetric ventricles: 0.984 and 0.956 respectively. Mean percent errors were 26.6% and 37.4% respectively. Only the correlation coefficient for symmetric ventricles was significantly lower for Model 3

than for Model 2; other values were not significantly different. With Model 4 (Table 1) the long axis area length method the correlation coefficient was excellent for symmetric ventricles: 0.972 but was substantially lower for asymmetric ventricles: 0.886; the latter value was also significantly lower than the corresponding value for Model 3. Mean percent errors were 30.9% for

CROSS SECTIONAL ECHO

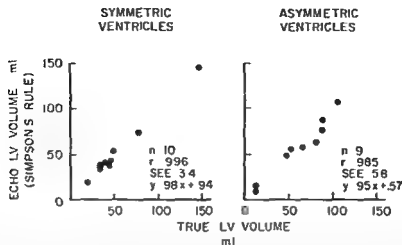


Fig 5 Comparison of volume in formalin fixed left ventricles, cross-sectional echocardiography (Simpson's rule Model 1) on the Y axis versus true volume on the X axis. A linear regression analysis was performed for calculated versus true volume the regression equation is shown. The correlation coefficients were excellent for both symmetric ($n = 10$) and asymmetric ($n = 9$) ventricles, 0.996 and 0.985 respectively. N = number of ventricles. r = correlation coefficient. SEE = standard error of estimate.

cles LV volume calculated by the above five models was compared to true fluid volume of the LV. Linear regression analysis was performed and standard error of estimate was calculated. Percent error was determined as follows:

$$\text{percent error} = \frac{\text{calculated LV volume} - \text{true LV volume}}{\text{true LV volume}} \times 100$$

For each of the five models, calculated LV volume was plotted against true LV volume. Percent errors were plotted and mean percent error was calculated as an average of absolute percent errors for the 10 symmetric and nine asymmetric left ventricles.

Results

For 10 symmetric hearts, the mean ratio of septal lateral diameter to anterior posterior diameter was 1.23 ± 0.06 (mean \pm SEM) and volume ranged from 19.5 to 146 milliliters. For nine asymmetric hearts, the mean ratio was 1.80 ± 0.07 and volume ranged from 13.0 to 105.5 milliliters.

Results of both linear regression and percent error analyses are summarized in Table I for all five mathematic models. Correlation coefficients and mean percent error are listed for a comparison between echo volume and true volume of the

formalin fixed left ventricle. The results of testing mathematic models 1 and 5 are graphically illustrated in Figs 5 and 6. Points are plotted for calculated volume versus fluid volume for 10 symmetric ventricles and for nine asymmetric ventricles. The regression equation, correlation coefficient, standard error of estimate, and mean percent error are listed for each model. With symmetric ventricles, excellent correlations were obtained for all mathematic models; correlation coefficients ranged from 0.996 to 0.967 and mean percent error ranged from 6.9% to 30.9%. Although reductions in r value with asymmetric ventricles were statistically significant for all five models, only in Models 4 and 5 did r values decline below 0.95.

Fig 5 shows a comparison between echo volume by the Simpson's rule (Model 1) on the Y axis and true volume on the X axis. The correlation coefficients were excellent for both symmetric and asymmetric ventricles, 0.996 and 0.985 respectively. Mean percent errors were low for both groups, 3.4% to 5.8% respectively.

With Model 2 (Table I), the short axis area length method, correlation coefficients were excellent for both symmetric and asymmetric ventricles, 0.993 and 0.974 respectively. Mean percent errors for Model 2 were low, 10.1% and 20.3% respectively. These values did not differ

lumen toward the base of the LV. Since the internal cavity structure of the formalin fixed left ventricle was not precisely the same as that of the normal left ventricle, the regression equation for each mathematic model may not be appropriate for application to the left ventricular volume in the beating heart. Nevertheless, the formalin fixed left ventricle is quite useful in evaluation of the relative merits of mathematic models for quantification of left ventricular volume. For Model 1 in particular, our results indicate that no regression equation is necessary in either symmetric or asymmetric ventricles; this is evident from the fact that the regression slopes (m) are very close to 1.0 and regression intercepts (I) are very close to zero (Table I).

In summary, this in vitro study of cross sectional echocardiography has demonstrated that volume of the symmetric left ventricle may be quantified reliably with all mathematical models tested, but volume of the asymmetric left ventricle is quantified most reliably by models that incorporate left ventricular length and either short axis area or two short axis diameters.

Summary

Cross sectional echocardiography was utilized for quantification of volume in 19 formalin fixed left ventricles in the presence or absence of ventricular symmetry, defined by the ratio of septal lateral to anterior posterior diameter. In 10 symmetric ventricles, this ratio was 1.23 ± 0.06 (mean \pm SEM), whereas in nine asymmetric ventricles the ratio was 1.80 ± 0.07 . Area, diameter and length measurements were obtained from short and long axis cross sectional images of the left ventricle and volume was calculated by five mathematical models previously described. To evaluate the reliability of each model, echocardiographic left ventricular volume was compared by linear regression and percent error analyses to directly measured fluid volume.

In symmetric ventricles, excellent correlations

($r = 0.996$ to 0.967) and reasonable mean percent errors (6% to 31%) were observed for all models in asymmetric ventricles. Models utilizing short axis area or two short axis diameters retained high correlation coefficients ($r = 0.985$ to 0.967) and similar mean percent errors, but standard formulas previously used with M mode echo angiography showed lower correlations ($r = 0.846$ to 0.873) and higher mean percent errors (37% to 54%). Thus, in the presence of ventricular asymmetry, analysis of short axis areas or diameters with cross sectional echocardiography is well suited for quantification of left ventricular volumes.

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symmetric ventricles and a substantially higher $\pm 21\%$ for asymmetric ventricles

Fig 8 shows a comparison between echo volume by the cube method (Model 5) on the Y axis and the true volume on the X axis. The correlation coefficient was very good for symmetric ventricles $r = 0.967$ in contrast the correlation coefficient was substantially lower for asymmetric ventricles $r = 0.873$. Mean percent error was substantially higher for asymmetric ventricles (53.5% versus 29.8%) than for symmetric ventricles.

Discussion

This study of cross sectional echocardiography demonstrates that volume can be accurately quantified in asymmetric as well as symmetric left ventricles using either short axis areas (Models 1 and 2) or two short axis diameters (Model 3) and ventricular length. Mathematical models of the present study were developed and tested in previous studies from this laboratory quantifying mass of the left ventricle in anesthetized dogs and volume in formalin fixed left ventricles. Models 1 and 2 utilizing short axis area and length of the left ventricle were developed specifically for cross sectional echocardiography. These models proved to be the most reliable for volume and mass quantification of the left ventricle by virtue of the high correlation coefficients, low mean percent errors and even distribution of regression points about the line of identity. The fact that Model 2 proved statistically to be just as reliable as Model 1 in the present study as well as in the LV mass study⁷ emphasizes the practical importance of the simple formula $V = 5/6 AL$ in both experimental and clinical application. Interestingly for asymmetric ventricles of the present study Model 3 ($V = \pi/6 D_1 D_2 L$) proved statistically to be just as adequate as Model 2 for LV volume quantification.

Model 4 the long axis area length method normally used with angiography and Model 5 the cube method used with M mode echocardiography were quite reliable for quantification of volume in symmetric ventricles but much less reliable in the presence of ventricular asymmetry. These findings of the present study are in general agreement with the findings of previous clinical studies of left ventricular volumes. In patients with symmetric myocardial wall motion good correlations were demonstrated between M mode

echocardiography and angiography but in patients with regional myocardial asynergy poor correlations were encountered indicating that estimation of asymmetric volumes from a single M mode echo dimension is unreliable. These observations reveal the major underlying assumption of Models 4 and 5 namely that the endocardial surface must be sufficiently symmetrical to be described as an ellipsoid. Because the manifestation of ventricular asymmetry due to myocardial ischemia or infarction is usually apparent only during the systolic phase of the cardiac cycle the major error in volume quantification occurs during systole.

Clinical application of these cross sectional echocardiographic mathematic models is dependent on the quality of short axis cross sectional images available in the human. If endocardial definition is adequate Models 1, 2 or 3 may account for the presence of ventricular asymmetry in the computation of left ventricular volume. Since it is difficult in patients to obtain adequate short axis images at more than one or two levels of the left ventricle Models 2 and 3 will probably be most applicable in the clinical situation. The ventricular asymmetry simulated in this study was a minor axis asymmetry generally consistent for the entire length of the left ventricle thus Models 2 and 3 utilizing measurements from only one minor axis section gave results only slightly less reliable than Model 1. Since dyssynergy due to regional myocardial ischemia or aneurysm may not extend the entire length of the left ventricle but may instead be localized (for instance to the apical half of the ventricle) Models 2 and 3 might tend to be less reliable than Model 1 unless the volume computations incorporate measurements from a minor axis section within the dyssynergic region. Thus the particular type of ventricular asymmetry used in this study may not have a specific clinical or physiologic analogy but the results of this study may nevertheless have general implications for volume quantification in the presence of ischemia, infarction, aneurysm or asymmetric hypertrophy.

The effects of formalin fixation procedures in the present study were reflected in minor changes of ventricular chamber characteristics: (1) some loss of prominence of papillary muscle projections into the ventricular cavity; (2) a smoothing effect on rough edges of the endocardial surface (trabeculae carneae); and (3) a constriction of the cavity

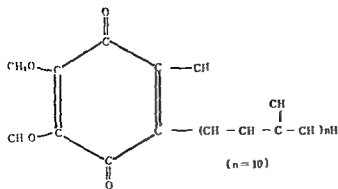


Fig 1 Chemical structure of coenzyme Q

Table 1 Chemical contents (w/w) in fatty acid emulsion

| | |
|----------------|-------|
| Linolenic acid | 0.77% |
| Linoleic acid | 5.16% |
| Oleic acid | 2.40% |
| Stearic acid | 0.44% |
| Palmitic acid | 1.24% |
| Egg yolk | 1.20% |
| Glycerin | 2.50% |

The chemical structure of coenzyme Q₁₀ is shown in Fig 1. Half of each group was observed for 40 minutes after the reperfusion of the preceding occlusion.

The method of the measurement of VMRT was described in detail previously.¹ In brief, a series of rectangular pulses (100 Hz, 1 msec in duration) were given throughout the ventricular vulnerable period with the electrode attached to a potentially nonischemic area of the left ventricle. The intensity of pulses was increased gradually until more than five extrasystoles occurred successively to obtain VMRT. In order to measure mitochondrial function, it is necessary to avoid the myocardial injury induced by any artifact such as regional burn by DC countershock. In many cases, less than 10 successive ventricular extrasystoles did not lead to ventricular fibrillation, and when the electrical stimulus was stopped, cardiac rhythm returned to normal without DC countershock. Therefore, we use VMRT instead of ventricular fibrillation threshold (VFT) as an index of arrhythmogenicity. Although VMRT was less than VFT, good reproducibility of this method was observed.

Venous blood was taken from the femoral vein, and blood pH, serum electrolytes, Na⁺, K⁺, Ca²⁺

Table II Indices of mitochondrial function 15 minute occlusion groups

| Groups | Saline + 15 min occ (n = 5) | Fatty acid + 15 min occ (n = 5) |
|--------|-----------------------------------|---------------------------------------|
| N | | |
| RCI | 4.25 ± 0.21 | 4.07 ± 0.30 |
| ADP/O | 1.99 ± 0.07 | 1.94 ± 0.04 |
| ATP | 582 ± 79.7 | 504 ± 63 |
| I | | |
| RCI | 3.34 ± 0.25 | 2.51 ± 0.37 |
| ADP/O | 1.97 ± 0.05 | n.d. |
| ATI | 468 ± 48.6 | n.e. |

(Mean ± SD)

nmol/mg protein/min

N: nonischemic area; I: ischemic area; n.d.: not detectable; n.e.: not calculated.

and Cl⁻ were measured. Throughout the experiment, Lead II of the ECG was monitored.

Canine hearts of another half of each group were isolated immediately after 15 or 30-minute occlusion, and myocardial mitochondria were prepared according to Hatefi's method.¹² In order to measure the respiratory control index (RCI) and ADP/O of the myocardial mitochondria, 1 ml of mannitol reaction mixture (0.3 M mannitol, 10 mM phosphate, 25 mM MgCl₂, 10 mM KCl, and 0.25 mM EDTA, pH 7.4) and 0.3 ml of the mitochondrial sample (10 mg mitochondrial protein per milliliter) were added together with 0.1 ml of potassium succinate (0.2 M) as a substrate, or 0.03 ml of ADP (0.01 M) as a substrate to the reaction cell mounted with the oxygen electrode (Kjussui Kagaku Ltd.).

ATP production rate (nmol/mg mitochondrial protein/minute) was calculated as 40 × oxygen consumption rate in State III ÷ mitochondrial protein/minute.

Results

In Fig 2, the time courses in VMRT in the 15 minute occlusion groups are shown. In the saline-infused group, the initial mean value of 1.59 ± 0.09 mA (mean ± SE) was significantly decreased to 1.13 ± 0.08 mA, 1.07 ± 0.08 mA, 0.75 and 15 minutes after ligation, respectively. Reduced VMRT, 1.18 ± 0.07 mA, was observed at 10 minutes after the release of ligation, however, at 20 minutes after the release, VMRT

Recovery time course of ventricular vulnerability after coronary reperfusion in relation to mitochondrial function in ischemic myocardium

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Although in 1937 Tennant and Wiggers noted a high incidence of ventricular arrhythmias (reperfusion arrhythmias) after the sudden restoration of blood flow to an occluded coronary artery in canine experiments and similar findings have been observed by other investigators reperfusion arrhythmias remain less familiar than the arrhythmias seen during acute coronary occlusion. However with the advent of coronary bypass surgery and with advances in coronary angiography indicating the relationship between coronary artery spasm and Prinzmetal's angina the subjects of ventricular arrhythmias and ventricular vulnerability to fibrillation following the release of a previously ligated coronary artery have attracted much interest and have been extensively studied in recent years. Nevertheless the mechanism whereby ventricular fibrillation is precipitated during reperfusion of ischemic myocardium remains uncertain.

We have studied^{1,2} the time courses in ventricular multiple response threshold (VMRT)

during coronary occlusion and after release of occlusion and have suggested that the recovery time course in VMRT closely relates to recovery of heart mitochondrial function following coronary reperfusion.

In this study the effects of the duration of occlusion time and infusion of fatty acid emulsion or infusion of coenzyme Q₁₀ on myocardial mitochondrial function were investigated in relation to the recovery time courses in VMRT following coronary reperfusion.

Methods

Forty-eight mongrel dogs of both sexes and weighing between 10 and 15 kg were anesthetized with sodium pentobarbital (50 mg/kg) intraperitoneally. Under artificial respiration the chest was opened in the fourth or fifth intercostal space and the heart was suspended in a pericardial cradle. A silk ligature was placed at the proximal branch of the left anterior descending coronary artery.

The dogs were divided into four groups (12 dogs each) according to the duration of coronary occlusion time and infusion of drugs.

Group 1 10 minute occlusion after saline infusion.

Group 2 15 minute occlusion after free fatty acid emulsion (contents are shown in Table I) 10 ml/kg infusion.

Group 3 30 minute occlusion after saline infusion.

Group 4 30 minute occlusion after coenzyme Q₁₀ 5 mg/kg infusion.

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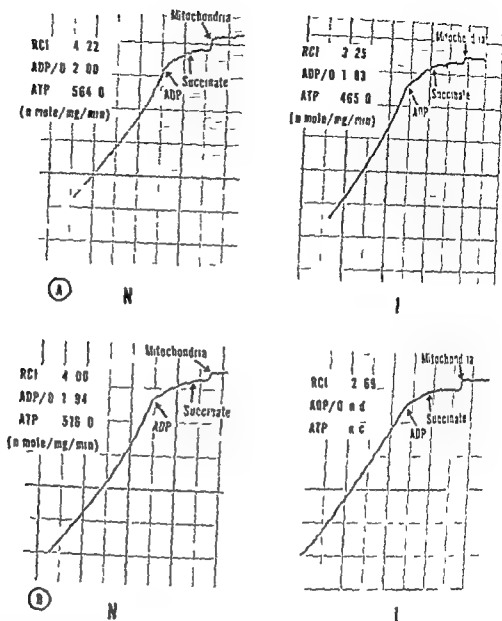


Fig 3 A and B Representative traces of mitochondrial respiration in the saline + 15 minute occlusion group (A) and in the fatty acids + 15 minute occlusion group (B). Infusion of fatty acids accelerated dysfunction of the mitochondria in the ischemic area.

The reduced value at 30 minutes was lowered significantly less than that in the saline infused group. At 10 and 20 minutes after reperfusion reduced VMRT 1.20 ± 0.07 mA and 1.38 ± 0.05 mA was observed respectively. However decrease in VMRT was less remarkable than that of the saline infused group. VMRT at 30 minutes after the release of ligation recovered to a value which is not significantly different from the preligation value.

These results showed us that it took 40 minutes after reperfusion in the saline infused group and 30 minutes in the fatty acid infused group to

recover the value of VMRT to that before ligation respectively.

Concerning the heart rate, blood pH and serum levels of Na, K, Ca, Cl, no significant changes were detected between the two groups.

Table III represents mitochondrial indices of 30 minute occlusion groups. As shown in the Table, mitochondria isolated from an ischemic area showed significantly lowered indices compared with those of nonischemic mitochondria. By 30 minute occlusion, ischemic mitochondria of the saline infused group showed further deterioration than those of the

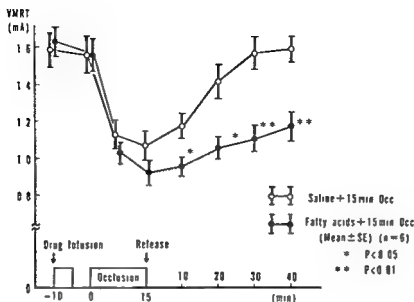


Fig 2 Time courses in VMRT of the 15-minute occlusion group. In the fatty acid infused group the recovery time course of VMRT was significantly retarded.

returned to a value which is not significantly different from that before ligation.

In the fatty acids-infused group the initial value of 163 ± 0.08 mA was not significantly decreased by fatty acid infusion itself. After ligation VMRT decreased significantly to 1.03 ± 0.06 mA at 7.5 minutes after ligation and to 0.92 ± 0.07 mA at 15 minutes after ligation. The reduced VMRT persisted i.e. 0.96 ± 0.05 mA, 1.06 ± 0.06 mA, 1.11 ± 0.07 mA and 1.18 ± 0.08 mA at 10, 20, 30 and 40 minutes after the release of ligation respectively. These reduced values were significantly lower than those of the saline infused group.

These results showed us that it took 20 minutes in the saline infused group and over 40 minutes in the fatty acid-infused group respectively to restore the value of VMRT to that before ligation.

Concerning the heart rate, blood pH and serum levels of Na, K, Ca, Cl, no significant changes were detected in the two groups.

Indices of mitochondrial function (RCI, ADP/O, ATP production rate) are shown in Table II. In both groups mitochondria isolated from an ischemic area showed significantly lowered RCI comparing with that of mitochondria isolated from a nonischemic area. It was noted that mitochondria isolated from an ischemic area of

the fatty acid-infused group showed significantly lowered indices compared with those of ischemic mitochondria of the saline infused group. Ischemic mitochondria of the fatty acid-infused group showed no reestablishment of the controlled respiration after the addition of ADP (Fig 3) i.e. by ischemia and more by fatty acid infusor myocardial mitochondria became loosely coupled showing little or no dependence of respiratory rate on ADP. Thus ADP/O and ATP production rate could not be calculated.

In Fig 4 the time courses in VMRT in the two 30 minute occlusion groups are shown. In the saline infused group the initial value of VMRT 1.56 ± 0.09 mA was decreased to 1.20 ± 0.07 mA, 1.06 ± 0.06 mA and 0.99 ± 0.05 mA at 10, 20 and 30 minutes after the ligation respectively. Reduced VMRT 1.02 ± 0.07 mA, 1.10 ± 0.08 mA and 1.23 ± 0.08 mA was observed at 10, 20 and 30 minutes after the release of ligation respectively while VMRT measured at 40 minutes after the release of ligation recovered to a value which is not significantly different from the preligation value. In the group infused with coenzyme Q (5 mg/kg) the initial value of 1.62 ± 0.07 mA was decreased to 1.21 ± 0.05 mA, 1.24 ± 0.05 mA and 1.21 ± 0.05 mA at 10, 20 and 30 minutes after ligation respectively.

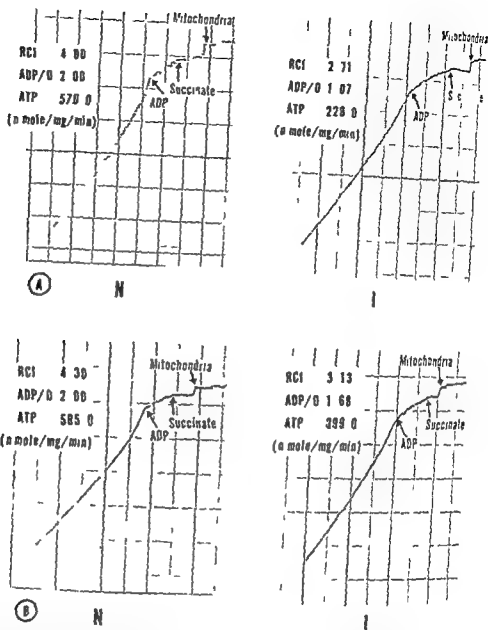


Fig 5 A and B Representative traces of mitochondrial respiration in the saline + 30 minute occlusion group (A) and in the coenzyme Q + 30 minute occlusion group (B) Coenzyme Q infusion prevented mitochondrial dysfunction induced by 30 minutes of ischemia

chondrial membrane, and the mitochondria to be loosely coupled. Coenzyme Q₁ isolated first by Crane and colleagues is an important factor of the mitochondrial electron transfer system as shown in Fig 7. Coenzyme Q transfers electrons from Complex I or II to Complex III. In the mitochondria obtained from the ischemic area, the electron transfer activity between Complex I and III was reduced, and the mitochondrial dysfunction induced by ischemia might be derived partly from this electron transfer disturbance. Administration of coenzyme Q preserved even if

not completely the activity of the electron transfer system and resulted in better mitochondrial function compared with controls (Table III).

It is interesting that the recovery time course VMRT of the saline + 15 minute occlusion group was similar to that of the coenzyme Q + 30 minute occlusion group. The recovery time course in VMRT of the fatty acid emulsion + 15-minute occlusion group was also similar to that of the saline + 30 minute occlusion group. These relationships of the two groups were also apparent in mitochondrial damage. In other words, the mit-

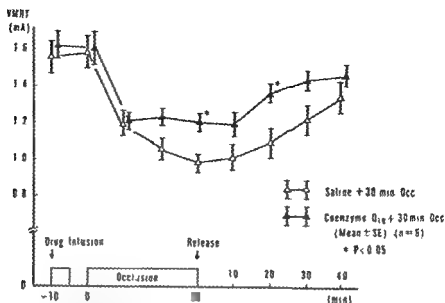


Fig 4 Time courses in VMRT of the 30-minute occlusion group. In the coenzyme Q₁₀-infused group recovery of VMRT was significantly shortened compared to that of the saline infused group

minute occlusion group (Tables II and III). However, these indices were significantly preserved by the administration of coenzyme Q.

Fig 5 shows representative traces of mitochondrial respiration in these two groups. It was also confirmed that the administration of coenzyme Q prevented mitochondrial dysfunction caused by ischemia.

Discussion

We have reported¹¹ that VMRT, which was lowered during coronary occlusion, recovered in the course of time after the release of ligation and that the recovery time course in VMRT depended upon the duration of the preceding occlusion time. But it remains obscure which factor truly affects the recovery time course in VMRT.

Our previous report¹¹ showed that the administration of fatty acid emulsion of 1 ml/kg did not cause mitochondrial dysfunction in the well oxygenated heart but accelerated the mitochondrial dysfunction induced by ischemia. The report also showed that the infusion of fatty acids delayed the recovery of VMRT. According to these results, we have suggested that mitochondrial function is one of the important determining factors of the recovery time course in VMRT.

As summarized in Fig 6 and Table IV, this experiment revealed that (1) the longer the duration of occlusion time, the longer was the neces-

Table III Indices of mitochondrial function in 30 minute occlusion groups

| Groups | Saline + 30 min occ (n = 6) | Coenzyme Q + 30 min occ (n = 6) |
|--------|-----------------------------|---------------------------------|
| N | | |
| RCI | 4.15 ± 0.25 | 4.24 ± 0.19 |
| ADP/O | 1.96 ± 0.04 | 1.90 ± 0.09 |
| ATP | 564 ± 30.1 | 549 ± 43.5 |
| I | | |
| RCI | 2.50 ± 0.38 | 3.28 ± 0.22 |
| ADP/O | 1.22 ± 0.34 | 1.69 ± 0.18 |
| ATP | 243 ± 90.3 | 402 ± 51.3 |

(Mean ± S.D.)
nmoles/mg prote n/m aut
N nonischemic area I ischemic area

sary recovery time in VMRT. (2) the longer the duration of occlusion time, the more severe was the mitochondrial damage caused. (3) fatty acid infusion accelerated mitochondrial damage induced by ischemia, and coenzyme Q₁₀ administration prevented the mitochondrial damage. (4) the recovery time in VMRT was in parallel with mitochondrial damage. As for mitochondrial function, myocardial ischemia suppressed the activity of the mitochondrial electron transfer system and β -oxidation cycle of fatty acids because of the accumulation of acyl CoA, which inhibits the ADP/ATP exchange reaction of mito-

Table IV Indices of mitochondrial function in all four groups

| | Mitochondria obtained from ischemic area | | |
|--|--|-------------|------------|
| | RCI | ADP/O | ATP |
| Saline + 15 min occ | 334 ± 0.25 | 1.97 ± 0.05 | 468 ± 48.4 |
| Coenzyme Q ₁₀ + 30 min occ | 378 ± 0.27 | 1.69 ± 0.18 | 407 ± 51.3 |
| Saline + 30 min. occ | 250 ± 0.38 | 1.27 ± 0.34 | 743 ± 97.3 |
| Fatty acids + 15 min occ | 251 ± 0.36 | nd | nc |

(M ± SD)

nmol/mg protein/minute

nd not detectable nc not calculated

severe the mitochondrial damage the longer was the necessary recovery time in VMRT

Any proposals as to possible mechanisms for the observed results must be highly speculative. However, if the depletion of cytosolic ATP which is produced mainly by mitochondria shortened the action potential duration as Cowan and Vaughn Williams reported the shortened duration of the action potential could be responsible for reentry in ventricular muscle and ventricular fibrillation. Therefore it is possible that mitochondrial function i.e. the rate of ATP supply is one of the important determining factors in the recovery time courses in VMRT.

Summary

This experiment was designed to investigate the effect of the duration of occlusion time and the infusion of fatty acid emulsion or that of coenzyme Q₁₀ on myocardial mitochondrial function and on the recovery time course in VMRT following coronary reperfusion. Forty-eight anesthetized mongrel dogs were divided into four groups based on the duration of the occlusion time and the infused drug. Group 1 was the saline + 15 minute occlusion group. Group 2 was the fatty acid emulsion (1 ml/kg) + 15 minute occlusion group. Group 3 was the saline + 30 minute occlusion group and Group 4 was the coenzyme Q₁₀ (3 mg/kg) + 30 minute occlusion group. After the drug administration (saline, fatty acid emulsion or coenzyme Q₁₀) the left anterior descending coronary artery was ligated for 15 or 30 minutes. In one half of each group canine hearts were isolated immediately at 15 or

30 minutes after ligation to prepare mitochondria. In the other half of each group, the ligation was released and coronary flow in reperfused VMRT was measured before arrest and after the ligation. The recovery time course of the saline + 15 minute occlusion group was similar to that of the coenzyme Q₁₀ + 30-minute occlusion group and the recovery time course of the fatty acid + 15 minute occlusion group was similar to that of the saline + 30 minute occlusion group. This relationship of the two groups is recognized in the mitochondrial damage. It is suggested that mitochondrial damage in other words energy supply dysfunction is one of the determining factors of recovery in VMRT after coronary reperfusion.

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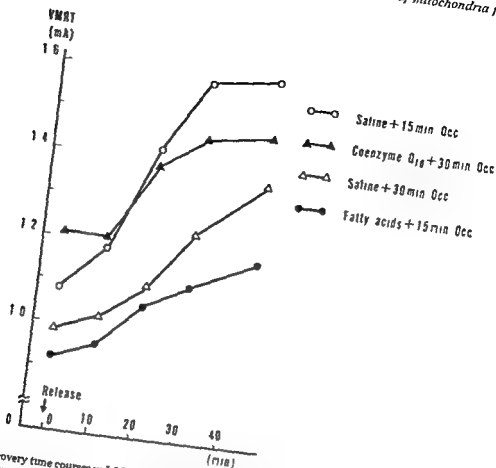


Fig 6 Recovery time courses in VMRT of all four groups. Recovery time course in the VMRT of the saline + 15-minute occlusion group was similar to that of the coenzyme Q₁₀ + 30-minute occlusion group and that of the saline + 30-minute occlusion group was similar to that of the fatty acid + 15 minute occlusion group.

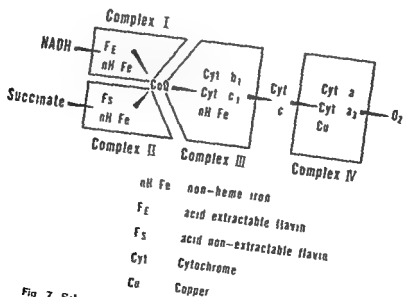


Fig 7 Schema of the mitochondrial electron transfer system

An electrocardiographic—pathologic correlative study on left axis deviation in hypertensive hearts

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Left axis deviation (LAD) has been generally ascribed to left anterior hemiblock (LAH) or left anterior focal block. While some investigators have attempted to find a correlation between LAD and LAH questions such as whether LAD is in fact consistent with LAH whether LAH is specific for LAD and what degree of LAD indicates LAH remain to be answered. Therefore we carried out a study to correlate LAD and conduction system pathology in autopsied hypertensive hearts with special reference to the left bundle branch (LBB).

Materials and methods

The well preserved hearts of 35 arterial hypertension patients (18 males, 17 females, ranging in age from 38 to 89 years) autopsied between 1970 and 1976 were studied and compared pathologically. Only specimens from essential (EH) and renal hypertension (RH) cases and cases with hypertension complicating aortic insufficiency (AI) are included in this study. The patients whose electrocardiograms (ECGs) showed left bundle branch block (LBBB) or myocardial infarction were excluded.

The materials were divided into three groups based on mean QRS axis calculated by the triaxial reference system in the frontal plane. Group 1

consisted of seven EH, three RH, and two AI cases with left axis deviation of -89 degrees to -30 degrees. In Group 2 there were eight EH, two RH and one AI with semi left axis deviation of -29 degrees to 0 degrees. Group 3 was composed of six EH, five RH and one AI with nonaxis deviation of 1 degree to 89 degrees.

After gross examination of the hearts, left ventricular volume was calculated according to the method of Lev and associates.¹

For histological examination of the atrioventricular conduction system, step sections were prepared according to a modification of the method of Lev and co-workers. In addition to the regular four blocks, three further blocks were obtained—i.e., one block each of the peripheral portions of the left anterior and posterior portions (LBB and LBB, respectively) and one block from the apex including the left and right ventricle and interventricular septum. From each block, five 7 micron thick slices were cut, stained with hematoxylin-eosin (HE), periodic acid-Schiff (PAS), and Elastic van Gieson (EvG) method and observed under a light microscope. If necessary, additional histologic sections were used.

Results

The ages and sex distribution of the patients, QRS axis, cardiac weights, and left ventricular measurements are shown in Table 1. Except for the QRS axis, there were no significant differences among the three groups. Incidence of LAD by ECG using criteria of Sokolow and Lyon² were 58% in Group 1, 73% in Group 2, and 83% in Group 3.

To compare severity of the lesions in the conduction system, four categories ranging from absent to severe were established (Table III). L

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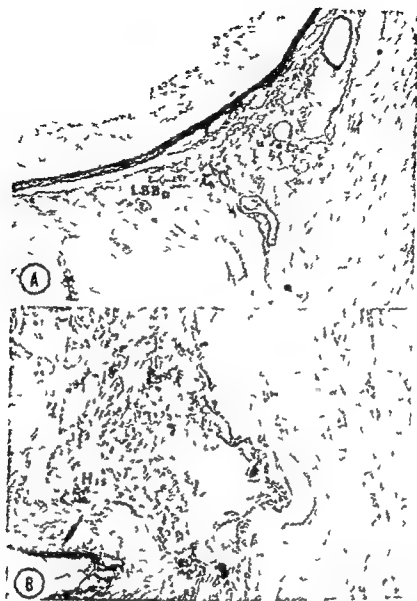


Fig 1 A A 40-year old male with fibrosis and fatty degeneration of the peripheral portion of the LBB (Elastic Van Gieson stain original magnification $\times 40$) B An 80 year old male with fibrosis of the His bundle (His) (Elastic Van Gieson stain original magnification $\times 40$) Both specimens are from Group 1

cells were intact at LBB₁ (Fig 4C) These findings were consistent with LAD

Case 3 A 58 year old male presented with aortic insufficiency and hypertension He died of congestive heart failure The ECG initially revealed the QRS axis to be -9 degrees (Fig 5A) at a later time the axis was noted to have shifted to the left and finally the axis was -30 degrees with junctional rhythm and slight widening of the QRS (Fig 5B) Histology revealed marked reduction of the conduction cells at LBB and LBB₂ due to entrapment by thickened subendocardial fibrous tissue (Fig 5C D E and F)

Case 4 A 43 year old female presented with

chronic renal failure (RH) While the QRS axis was normal at 43 degrees (Fig 6A) both anterior and posterior radiations of the LBB were damaged by marked fibrosis and fatty infiltration (Fig 6B and C)

Discussion

1 Extent of LAD in LAH To our knowledge, no genuine studies on the correlation between the electrocardiographic and pathologic findings have been published and there is no consensus regarding the extent of LAD which is compatible with LAH

Demoulin and Kulbertus reported a correlation

Table I Comparison of the three groups based on QRS axis and gross pathological findings

| Group | No of cases | Sex | | Age (years) | Electrical axis (°) | Cardiac weight (g) | Left ventricle | |
|-------|-------------|-----|---|-------------|---------------------|--------------------|----------------|-------------|
| | | M | F | | | | Thickness (mm) | Volume (mL) |
| 1 | 17 | 6 | 6 | 63.4 ± 14.8 | -40.1 ± 8.9 | 441 ± 1.6 | 13.4 ± 3.1 | 21.8 ± 19.1 |
| 2 | 11 | 6 | 3 | 69.3 ± 4.9 | -16.4 ± 6.2 | 399 ± 7.6 | 14.4 ± 2.1 | 14.2 ± 6.5 |
| 3 | 19 | 6 | 6 | 67.0 ± 14.9 | -46.3 ± 18.6 | 447 ± 11.7 | 14.1 ± 1.9 | 19.6 ± 12.0 |

Mean ± standard deviation

Table II Severity of the lesions in the conduction system

| Group | His bundle | | | | LBB | | | | LBB | | | |
|-------|------------|---|----|-----|-----|---|----|-----|-----|---|----|-----|
| | 0 | + | ++ | +++ | 0 | + | ++ | +++ | 0 | + | ++ | +++ |
| 1 | 6 | 4 | 0 | 2 | 2 | 5 | 4 | 1 | 0 | 2 | 1 | 9 |
| 2 | 5 | 3 | 4 | 0 | 2 | 6 | 1 | 2 | 3 | 4 | 2 | 2 |
| 3 | 7 | 4 | 1 | 0 | 4 | 4 | 1 | 3 | 1 | 8 | 2 | 3 |

LBB = left bundle branch (p posterior & anterior)

Degree of severity 0 normal + mild ++ moderate +++ severe (severe lesion means reduction of the conduction cells more than 50%)

Table III Histological findings of the conduction system and incidence of severe lesions

| Group | His bundle | | | Posterior radiation (LBB _p) | | | Anterior radiation (LBB _a) | | | |
|-------|------------|---------------|-------|---|--------------|-------|--|--------------|----------|-------|
| | Fibrosis | Calcification | Total | Fibrosis | Degeneration | Total | Fibrosis | Degeneration | Bleeding | Total |
| 1 | 1 | 1 | 2 | 1 | 0 | 1 | 5 | 2 | 2 | 9 |
| 2 | 3 | 0 | 3 | 1 | 1 | 2 | 1 | 1 | 0 | 2 |
| 3 | 0 | 0 | 0 | 2 | 1 | 3 | 7 | 1 | 3 | 13 |

This table severe lesion means reduction of conduction cells by more than 50%. One of our group Okada⁷ based upon his numerous electrocardiographic pathologic correlation studies recognized as empirical evidence that 50% reduction of conduction cells almost always shows some kind of conduction disturbance. Therefore we may call severe lesions with over 50% reduction of conduction cells at LBB anatomical LAH.

In Group 1, nine of 12 (75%) specimens showed severe lesions at LBB; one of these had lesions at both LBB and LBB_p, and another one showed severe lesions at the peripheral portion (Fig 1A). There were also two cases with severe lesions at the bifurcation of the His bundle (Fig 1B); the ECG showed right bundle branch block (RBBB). In this group there was one case without severe lesions in the conduction system; the electrical axis was -35 degrees. In Group 2 there were two cases each with severe lesions at both radiations; and in Group 3 there were three similar cases.

The incidence and site of severe lesions is shown in Table III. In the 35 specimens, fibrosis (Fig

2A) at the His bundle, LBB or LBB_p was noted in 13 (37%); degeneration was found (Fig 2B) in six (17%); bleeding (Fig 2C) was seen in two (6%); and calcification (Fig 2D) was noted in one (3%). As for the relationship between the type of hypertension and severe lesions, fibrosis was noted most frequently in EH (38%) and degeneration in RH (60%).

Case reports

Case 1 An 89-year-old female presented with polycystic kidney (RH) and a QRS axis of -45 degrees (Fig 3A). Histology revealed the subendocardial connective tissue to be thickened and to interrupt the conduction cells of LBB almost completely (Fig 3B and C). At the LBB, there was mild fibrosis at the proximal portion and the conduction cells were hypertrophic.

Case 2 A 77-year-old female presented with subarachnoid hemorrhage (EH) and a QRS axis of -58 degrees (Fig 4A). Histology revealed massive bleeding at LBB (Fig 4B) and slight bleeding under the subendocardium. The conduction

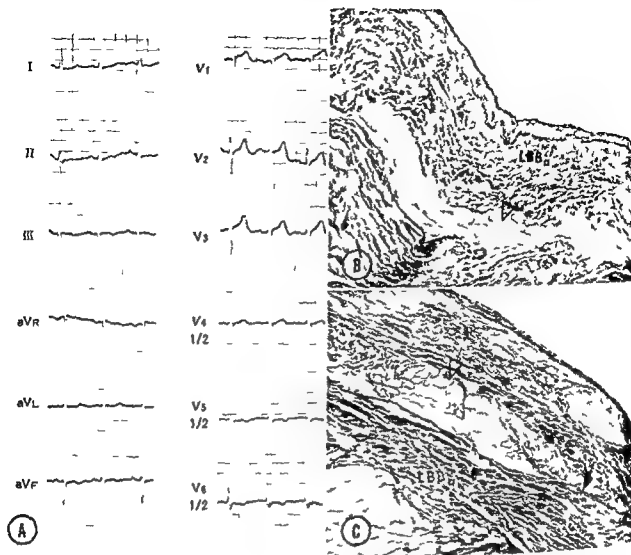


Fig 3 Case 1 A Electrocardiogram B Proximal portion of the LBB C Somewhat distal portion of the LBB Thick fibrosis (solid arrows) interrupts the conduction cells (open arrows) (Elastic Van Gieson stain original magnification $\times 40$)

and LAH. Although we used the step sectioning (semi serial) method rather than the serial sectioning method, our study fulfils the proposed criteria for a genuine correlative study.

2 LAD in LAH. Conduction delay at LBB is thought to effect LAD in LAH.^{11,12} Focal lesions at the His bundle which effect longitudinal dissociation¹³ produce LAD and RBBB.^{14,17} In our series there were two such cases. Since the bifurcation of the His bundle can be considered to represent the proximal portion of LBB, a block of that portion can be regarded as modified LAH and LAD in LAH can be ascribed to conduction delay at LBB.

3 A concept of cancellation. In the present series, there were one Group 1, two Group 2 and

three Group 3 cases with severe lesions at LBB and LBBB. To answer the questions as to why the spectrum of the mean QRS axis in the frontal plane was so wide despite similar changes at both radiations and why complete LBBB did not occur we propose two hypotheses. First conduction disturbances are not always either severe or complete rather in some cases a conduction delay occurs. Our second hypothesis is that axis deviation is produced by differences in conduction velocity between the two divisions. From these points of view the distribution of the QRS axis is summarized as shown in Table IV. Only complete conduction block of both divisions yields LBBB and LAD occurs in cases of complete conduction block of LBB or slower conduction at the LB

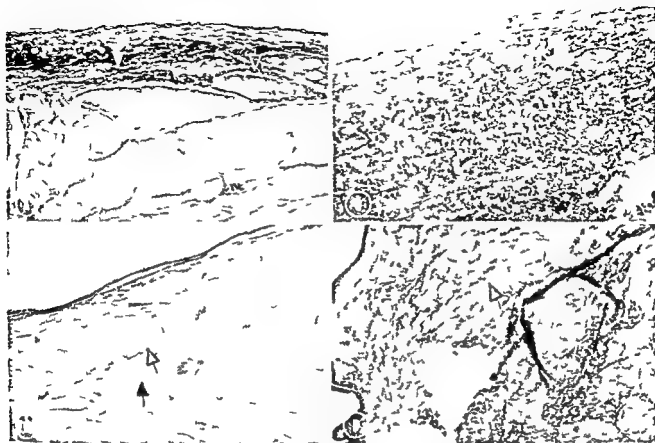


Fig 2 Histologic findings in severe lesions. A A 1 year old male from Group 1 with fibrosis at LBB (solid arrow) (Elastic Van Gieson stain original magnification $\times 40$). B A 38-year-old male from Group 3 with vacuolization and edema at LBB (solid arrow) (Elastic Van Gieson stain original magnification $\times 40$). C A 60-year old female from Group 1 with bleeding at LBB (Hematoxylin and eosin stain original magnification $\times 40$). D An 85 year old male from Group 1 with calcification (solid arrow) of the central fibrous body at the His bundle (Elastic Van Gieson stain original magnification $\times 40$). Open arrows indicate conduction cells in A, B and D.

tive study on the conduction system and LAD. They found that nine of 10 cases had severe LBB lesions and five of these showed predominant lesions at the anterior subdivision. However as their series included some myocardial infarction cases we do not consider theirs a genuine correlative study linking ECG pattern and the conduction system. For the same reason we have our reservations about the study reported by Entman and associates.

There are two well known criteria in ECG for LAH. One is LAD in excess of -45 degrees as postulated by Rosenbaum and co workers and another is LAD in excess of -30 degrees as set down by Kulbertus and colleagues and by Gopal.¹¹ In our series defining severe lesion over 50% reduction of conduction cells at LBB as

anatomical LAH and by using the former criterion sensitivity (true positives/true positives + false negatives) was 25% (four out of 16) and specificity (true negatives/true negatives + false positives) was 100% (19 out of 19) and using the latter criterion sensitivity 69% (11 out of 16) and specificity 95% (18 out of 19). While in the criterion of Rosenbaum and associates specificity was high but sensitivity low we think that the criterion of Kulbertus and associates¹⁰ and of Gopal¹¹ is more appropriate.

We propose that serial sections control materials and relatively uniform specimens from patients without other heart disease such as myocardial infarction or congenital heart disease which may affect the QRS axis should be the criteria for a genuine correlative study on LAD.

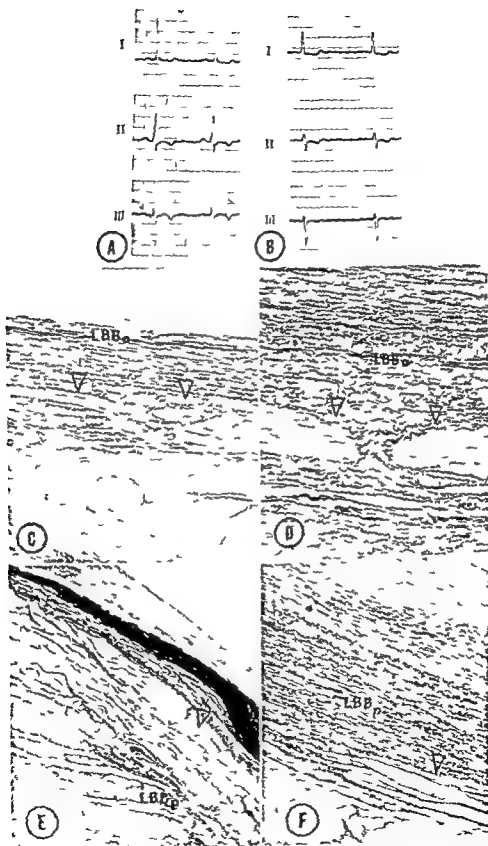


Fig 3 Case 3 A Electrocardiogram on Oct 25, 1972 B Electrocardiogram on July 10, 1973 C Histologic section shows reduction of conduction cell (Elastic Van Gieson stain original magnification $\times 40$) D Thick fibrous tissue shows the LBB (Elastic Van Gieson stain original magnification $\times 100$) E Proximal portion of LBB, showing preserved conduction cell (Elastic Van Gieson stain original magnification $\times 40$) F Thick fibrous tissue interrupts the conduction cell of LBB at the distal portion of E (Elastic Van Gieson stain original magnification $\times 40$) Open arrows indicate conduction cells in C to F

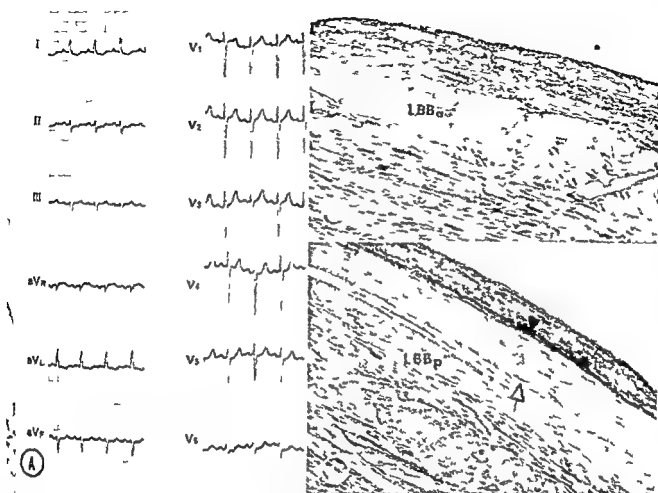


Fig 4 Case 2 A Electrocardiogram B Massive bleeding at the LBB (Hematoxylin and eosin stain original magnification $\times 40$) C Slight bleeding (solid arrow) under the subendocardium. Conduction cells (open arrow) are intact at LBB_p. (Elastica Van Gieson stain original magnification $\times 40$)

than at LBB_p. In the same conduction delay of both divisions each cancels the axis deviation of the other (cancellation). In cancellation LBBB does not occur because of preservation of conduction in the LBB although it is slow and the QRS axis remains in the normal range. In such cases slight prolongation of the QRS axis may occur. We may explain from our hypotheses that in some of the Group I cases LAD occurred because conduction disturbance was not complete and conduction velocity at LBB was slower than at LBB_p although severe lesions were present at both divisions. Furthermore five cases of Groups 2 and 3 in which the conduction delay in both divisions was almost the same did not show LAD possibly because of cancellation between LBB

and LBB_p. While there is no consensus as yet regarding the concept of cancellation it represents an important hypothesis which is based on our control study and it should be pursued further.

4 The two versus three division theory in LBB. Our hypothesis regarding the LBB divisions is based on the consideration that there are two main portions consisting of the anterior and posterior radiation. Demoulin and Kulbertus¹ and Massing and James² stated that the septal division is between the two main radiations. However histologically the septal division appears to be a part of the posterior radiation with cellular communications between it and the posterior radiation. Based on this consideration

Table IV Relationship between QRS axes and mode of conduction in LBB

| Radiation | LBB ₁ | | | | |
|-----------|--------------------|--------|------|--------|-------|
| | Mode of conduction | Normal | Slow | Slower | Block |
| LBB | Normal | NAD | PAD | RAD | RAD |
| | Slow | LAD | C | RAD | RAD |
| | Slower | LAD | LAD | C | RAD |
| | Block | LAD | LAD | LAD | LBBB |

† Normal normal conduction. Slow slow conduction velocity. Slower slower conduction velocity. Block complete conduction disturbance. C cancellation. NAD nonaxis deviation. RAD right axis deviation.

LAD and RAD partly include QRS axes with tendency of LAD and PAD respectively.

investigated portions more peripherally located than the blocks of Lev and colleagues' method, our materials were comprised of relatively uniform hypertensive cases, and we included control materials. Therefore we consider our results to be reliable for evaluating the pathology of the conduction system in hypertensive hearts.

Summary

We performed an electrocardiographic pathologic correlative study using the step sectioning method in 35 autopsy specimens from patients with hypertension.

Eleven out of 12 cases (91.7%) in Group 1 had severe lesions at LBB or the His bundle and we propose that LAD in excess of -30 degrees is a good criterion in hypertension for LAH.

There were six cases in all with severe lesions at both radiations of the LBB. In one case of Group 1 LAD was suggested to be due to slower conduction at the LBB than at the LBB₁ and findings in five cases of Groups 2 and 3 led us to speculate that there was no LAD because of cancellation between the LBB and the LBB₁.

Histopathology revealed fibrosis, degeneration, bleeding and calcification which pathogenetically may derive from mechanical strain effected by hypertension and metabolic changes in cases with chronic renal failure.

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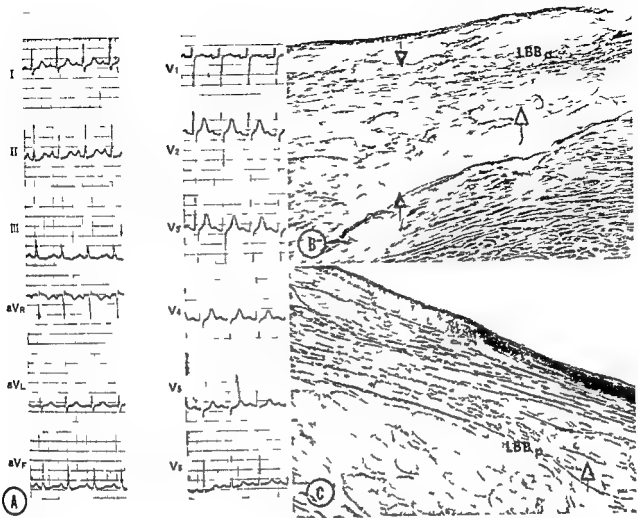


Fig 6 Case 4 A Electrocardiogram B Fatty degeneration and fibrosis (solid arrows) at LBB (Elastica \an Gieson stain original magnification $\times 40$) C Marked fibrosis at LBB (Elastica \an Gieson stain original magnification $\times 100$) Open arrows indicate conduction cells

we evaluated our data according to the two division theory

Conduction system morphology Regarding the cause of conduction disturbances Lev proposed sclerosis of the left side of the cardiac skeleton and Sugura and co workers suggested mechanical strain because they found that mucopolysaccharides were increased in the fibrotic area In hypertension mechanical strain strongly affects the interventricular septum leading to hypertrophy of the septal wall which may lead to conduction disturbances due to compression of the conduction system

All materials in the present series were from patients with hypertension and seven of 12 (58%) of Group I specimens revealed fibrotic changes in the conduction system indicative of accumulated

mechanical strain Degenerative changes were present in 60% of RH cases suggesting that metabolic changes due to chronic renal failure produced edema and fatty infiltration in the conduction system The massive bleeding into LBB which produced LAD in two of our present cases appears to have been due to rupture of weakened small vessels induced by mechanical strain in the septal wall The presence of a focal increase in catecholamines or other vasoactive substances is probable in these cases

6 Step sectioning method While we used the step (semi serial) sectioning method rather than the more precise serial sectioning method pathological changes occur in relatively narrowly circumscribed areas of the conduction system and our sections included these Moreover we also

electrodes was introduced through the sheath and under fluoroscopic control was advanced into the right ventricle. After satisfactory positioning the outer sheath was either left in place in the femoral vein or was withdrawn and secured. All patients remained at bed rest while the pacing electrode was in place.

Fibrinogen scan One hundred microcuries of ^{51}I labelled fibrinogen was injected intravenously and a scan was performed in both lower extremities prior to the electrode insertion¹¹; the scan was then repeated daily. The test was considered positive when the radioisotope counts on two consecutive days were more than 20% of the baseline precordial measurements¹². In addition a disparity in counts of more than 20% between two areas on the legs was considered positive. The test was interpreted as negative when the counts were unchanged. Counts that were between 10% and 20% of control and counts that were elevated for less than 24 hours were considered equivocal.

Assay of fibrin degradation products Blood for the preparation of serum was collected into thrombin and epsilon amino caproic acid. The staphylococcal clumping test method was used¹³ employing bacterial preparations sensitive to 0.75 $\mu\text{g}/\text{ml}$ of fibrinogen. A concentration of less than 8 $\mu\text{g}/\text{ml}$ was considered normal¹⁴.

Impedance plethysmography All studies were performed by the same trained technician using the cuff occlusive technique and a cuff occlusion time of sufficient duration to obtain optimal filling¹⁵. The maximum rise on the plethysmographic recording during cuff inflation and the fall in three seconds following cuff deflation were determined. From these findings a numerical figure representing the venous function index was derived. On the basis of the venous function index score the results were interpreted as positive, negative or equivocal.

Venography Venography on the affected leg was performed in four patients with equivocal findings in the noninvasive tests. In the remaining patients in this category venography could not be performed because of the unwillingness of the patient or his physician. The studies were evaluated by two independent radiologists.

Results

The patient population consisted of 12 men and eight women. The average age was 71 years (range 33 to 86 years). In 18 patients the right

femoral vein was used in two patients the left femoral vein was used.

Incidence Of the 20 patients evaluated, 13 patients (25%) fulfilled the criteria for deep vein thrombosis (Table I). One had positive findings on all of the noninvasive tests. There were 11 patients with equivocal abnormalities on the noninvasive tests. Four of these underwent venography and all four had positive venograms. Of these one had thrombosis of the femoral vein, one had thrombosis in several calf veins and one had thrombosis in both the thigh and calf veins. The fourth patient had thrombosis of the entire deep venous system of the extremity. This patient was the only one who had clinical evidence of deep vein thrombosis.

Tests performed on the contralateral extremity were consistently negative except in one patient in whom the fibrinogen scan was positive and another in whom the impedance plethysmography was positive. Neither of these patients had evidence of deep venous thrombosis in their catheterized leg.

Clinical background The clinical background of the patients is shown in Table I. Patients with deep vein thrombosis did not differ from those without thrombosis with regard to recent myocardial infarction, type of heart disease or history of congestive heart failure.

Technical aspects related to the pacing procedure The number of venopunctures used for the introduction of the electrode varied from one to 10 but in 15 cases fewer than three punctures were necessary. A new electrode was used in 12 cases and the introducer sheath was pulled out in 16 cases. The length of time that the pacing catheter remained in place varied from one to 11 days with an average period of 3.4 days.

There was no relationship between the occurrence of deep vein thrombosis and the number of venopunctures, the presence of the outer sheath in the femoral vein or the duration of electrode use. None of the patients in whom an old electrode was used developed thrombosis.

Clinical sequelae None of the patients showed evidence of local or systemic infection. There were no clinical features suggestive of pulmonary embolism in any of the patients.

Discussion

The transfemoral approach provides a relatively simple and rapid technique for temporary pac-

Transfemoral temporary pacing and deep vein thrombosis

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Transfemoral placement of a pacing catheter is a widely employed approach for temporary pacing.^{1,2} Few complications of this technique have been reported among which deep vein thrombosis has been only rarely mentioned.³ The clinical diagnosis of deep vein thrombosis has been shown to be unreliable.⁴ The development of reliable noninvasive tests^{5,6} has provided the opportunity to evaluate the incidence of deep vein thrombosis associated with transfemoral pacing. The diagnosis of deep vein thrombosis was based on I fibrinogen scanning, impedance plethysmography and measurement of fibrin degradation products in all patients. In four patients venography was also performed.

Materials and methods

Patients who would require a temporary pacemaker for a minimum of 24 hours were studied. Patients who were critically ill who were on anticoagulant therapy or who had a history of previous venous disease, thromboembolic disease or hemoglobinopathies were excluded from the study. During the period May 1978 to March 1979, 20 patients were studied after obtaining informed consent. Prior to the insertion of the pacemaker electrode, I fibrinogen was injected. Impedance plethysmography was performed on both extremities and blood was drawn for fibrin degradation products. Following pacer insertion,

the fibrinogen scan and assay of fibrin degradation products were obtained daily and impedance plethysmography was performed on alternate days. Two observers made daily recordings of the presence or absence of leg pain, edema, tenderness, change in leg and thigh circumference and Homans sign. A study was terminated three days following the removal of the electrode unless the tests were positive at that time in which case they were continued until the tests returned to normal. Whenever possible, venography was performed in patients with equivocal results in the noninvasive tests. Clinical information regarding the patients was not provided to the investigators analyzing the diagnostic tests.

Based on the findings of clinical observation, fibrinogen scan, assay of fibrin degradation products, impedance plethysmography and venography, the following criteria were used to establish the diagnosis of deep vein thrombosis—*Present* venogram was positive or three of the other parameters were positive. *Absent* venogram was negative or three of the other parameters were negative. *Equivocal* results in neither of the above two categories.

Method of electrode insertion. Pacing was performed via the transfemoral route with a No. 5 bipolar catheter by a modified Seldinger technique. An 18 gauge thin walled needle was used to puncture the femoral vein. A guidewire with a flexible tip was inserted through the needle and the needle was then replaced by a short Teflon inner catheter. An outer dilating sheath was passed over the inner catheter. The guidewire and the inner Teflon catheter were removed leaving only the outer sheath in the femoral vein. A woven Dacron catheter with bipolar platinum

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and restriction of venous flow might have contributed to the genesis of the thrombosis.

The patients with thrombosis did not differ clinically from those without deep vein thrombosis. There was no relationship between the occurrence of deep vein thrombosis and the number of venepunctures or the presence of the introducer sheath in the femoral vein. Our data are insufficient to derive a definite conclusion regarding the effect of the state of the electrode on the occurrence of thrombosis. However, none of the eight patients in whom an old sterilized electrode was used demonstrated deep vein thrombosis. The occurrence of thrombosis did not seem to be influenced by the duration of pacing, although all those with documented deep vein thrombosis had the electrode in place for at least 48 hours.

The clinical significance of deep vein thrombosis in these patients is unclear. None of our patients developed clinical evidence of pulmonary embolism. One patient, however, suffered severe temporary disability resulting from thrombosis of the entire venous system of the extremity used for pacing. Some studies have demonstrated a high incidence of asymptomatic pulmonary emboli in patients with positive fibrinogen leg scan. Others have questioned whether asymptomatic clotting in the veins of the lower leg has any serious sequelae.

In conclusion, deep vein thrombosis is a common complication of transfemoral pacing. Although clinical symptoms are infrequent and adverse long term sequelae have not been demonstrated, the high incidence of venous thrombosis with transfemoral pacing should be considered before deciding upon the site of entry for a temporary pacemaker. Careful prospective analysis of the complications of the use of other entry sites will be necessary in order to make a rational choice. Further studies are also necessary to determine if deep vein thrombosis associated with transfemoral pacing can be prevented by anticoagulants or other means.

Summary

The incidence of deep vein thrombosis following transfemoral temporary pacing was prospectively assessed in 20 consecutive patients using serial ¹²⁵I fibrinogen scanning, impedance plethysmography, and measurements of fibrin degradation products. Four patients underwent venography. Of the twenty patients, five (25%) had

definite evidence of deep vein thrombosis, as demonstrated equivocal abnormalities and no had no evidence of thrombosis. Thrombosis was found only in the legs used for pacing. Of the five with deep vein thrombosis, one had positive findings in all the noninvasive tests. Venography confirmed the diagnosis in the other four. One had thrombosis of the femoral vein, one had thrombosis of several calf veins, and one had thrombosis of both the thigh and calf veins. The fourth patient had thrombosis of the entire deep venous system of the leg. This latter patient was the only one who had clinical evidence of venous thrombosis. The patients with deep vein thrombosis did not differ in clinical characteristics from those without thrombosis. There was no relationship between the occurrence of deep vein thrombosis and the number of venepunctures, the state of the electrode, the presence of the introducer sheath in the femoral vein, or the duration of pacing.

In conclusion, deep vein thrombosis is a common complication of transfemoral temporary pacing and the high incidence of its occurrence should be considered before deciding upon the site of entry for a temporary pacemaker.

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Table 1 Clinical data and results

| Case no | Sex | Age | Clinical background | No of Punct | Electrode (new/old) | Sheath (in/out) | Duration electrode (days) | Clinical DVT | FS | IPG | FDP | Veno gram | Conclu sion |
|---------|-----|-----|---------------------|-------------|---------------------|-----------------|---------------------------|--------------|-----|-----|-----|-----------|-------------|
| 1 | M | 4 | CAD AMI VT | 1 | New | In | 5 | Neg | Pos | Pos | Pos | Pos | Pos |
| 7 | M | 52 | CAD Old MI VT | 4 | New | Out | 4 | Neg | Pos | Neg | Pos | Pos | Eqv |
| 3 | M | 33 | VHD HB | 1 | New | Out | 10 | Neg | Neg | Neg | Neg | Neg | Neg |
| 4 | F | 5 | CAD Old MI | 7 | New | Out | 2 | Neg | Eqv | Eqv | Eqv | Eqv | Eqv |
| 5 | M | 50 | HB | 1 | New | Out | 1 | Neg | Neg | Neg | Eqv | Neg | Neg |
| 6 | M | 74 | CHF VT | 1 | New | Out | 8 | Neg | Neg | Eqv | Pos | Eqv | Eqv |
| 8 | F | 79 | HB | 1 | Old | Out | 2 | Neg | Neg | Neg | Neg | Neg | Neg |
| 8 | M | 50 | CAD Old MI VT | 2 | New | Out | 3 | Neg | Neg | Neg | Eqv | Neg | Neg |
| 9 | M | 81 | CAD Old MI | 1 | New | Out | 2 | Neg | Neg | Pos | Eqv | Pos | Pos |
| 10 | M | 82 | HB | 1 | New | Out | 3 | Neg | Eqv | Eqv | Pos | Pos | Pos |
| 11 | F | 86 | A FIB | 2 | Old | Out | 4 | Neg | Neg | Eqv | Pos | Eqv | Eqv |
| 12 | M | 8 | CHF HB | 2 | Old | Out | 1 | Neg | Neg | Neg | Pos | Neg | Neg |
| 13 | F | 8 | HB | 1 | New | Out | 3 | Neg | Neg | Neg | Pos | Neg | Neg |
| 14 | F | 69 | HB | 1 | Old | In | 1 | Neg | Pos | Eqv | Eqv | Eqv | Eqv |
| 15 | F | 7 | HB | 5 | Old | In | 1 | Neg | Neg | Pos | Pos | Eqv | Eqv |
| 16 | M | 86 | Ca A FIB | 1 | Old | In | 2 | Neg | Neg | Neg | Pos | Neg | Neg |
| 17 | F | 6 | HB | 2 | Old | Out | 1 | Neg | Neg | Neg | Neg | Neg | Neg |
| 18 | M | 71 | A FIB | 6 | New | Out | 4 | Pos | Neg | Pos | Pos | Pos | Pos |
| 19 | M | 4 | HB VT | 10 | Old | Out | 1 | Neg | Neg | Eqv | Eqv | Neg | Neg |
| 20 | F | 77 | CHF HB VT | 2 | New | Out | 6 | Neg | Pos | Neg | Pos | Pos | Pos |

Pos = positive; Neg = negative; Eqv = equivocal; Punct = puncture; FS = fibrinogen scan; IPG = impedance plethysmography; FDP = fibrin degradation products; DVT = deep vein thrombosis; CAD = coronary artery disease; CHF = congestive heart failure; MI = myocardial infarction; AMI = acute myocardial infarction; VT = ventricular tachycardia; HB = heart block; A FIB = atrial fibrillation; VHD = valvular heart disease; Ca = coronary artery disease.

Abnormal in contralateral leg

It is widely employed since it is thought to be relatively free of complications. Despite the frequent use of this approach, reports of deep vein thrombosis of the lower extremities are uncommon. In a retrospective series of 80 patients, Cohen and associates noted the occurrence of deep vein thrombosis in five patients. Of 267 patients with transfemoral pacing reported by Furman and co-workers, only one was found to have had clinical evidence of iliofemoral phlebitis. In several other large series of consecutively paced patients using the transfemoral route, no instance of deep vein thrombosis was noted.

Our study demonstrates a high incidence of venous thrombosis as a complication of transfemoral pacing. The diagnosis was made in five of 20 patients studied. Only one patient had positive findings in all of the noninvasive tests. There were 10 patients with equivocal abnormalities in the noninvasive tests of whom only four underwent venography; all four had thrombosis of the deep venous system. It is possible that some of the remaining patients with equivocal results in the

noninvasive studies might have demonstrated deep vein thrombosis had venography been performed. Thus the incidence of thrombosis might indeed be higher than the 25% noted. The rarity of reports of thrombotic complications is probably due to the fact that thrombosis is usually not clinically apparent. In our study, only one patient had symptoms and physical findings suggestive of deep vein thrombosis.

The occurrence of deep vein thrombosis can be attributed to several factors associated with routine transfemoral pacing. These include: venepuncture, the presence of a foreign body, partial venous obstruction, and extended periods of bed rest. Infection can be a cause of thrombosis, but this did not appear to be a factor in these cases. Although our patients remained at bed rest, mobility of the extremity used for pacing was not selectively limited, yet deep vein thrombosis occurred only in the extremity used for pacing. It is noteworthy that all our patients who had venograms had clots distal to the site of entry of the electrode. Thus partial venous obstruction

The effects of vasoconstriction on experimental coronary artery stenosis

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There is little doubt at present that coronary artery spasm is an important mechanism in the production of angina pectoris. Several recent studies have also demonstrated the presence of coronary spasm in preexisting atherosclerotic lesions of the coronary arteries and have suggested that spasm may be responsible for myocardial infarction in some patients.¹⁻³ Implicit in these clinical observations is the ability of large proximal coronary arteries to constrict and thereby alter their luminal area. From postmortem examination, Maser and colleagues demonstrated that areas of stenosis often contain an arterial wall segment which is normal and apparently able to contract. To properly study this type of lesion we have developed an *in vitro* arterial preparation which resembles hemodynamically the coronary lesion in man. This model is achieved by obstructing flow through the artery with an intraluminal device which allows a stenosis to be created while still allowing arterial vasoconstriction to occur. When the effects of active arterial vasoconstriction were examined in this model in the presence of an otherwise mild fixed stenosis, a striking alteration in the hemody-

namics of the stenosis was noted. In effect the partial stenosis even when mild caused severe occlusion in the presence of arterial vasoconstriction. This finding provides some insight into the effects of spasm on coronary flow in man.

Methods

The effects of arterial vasoconstriction on the hemodynamics were examined in an *in vitro* coronary artery preparation. An *in vitro* preparation was used to eliminate distal coronary vasculature, renal, humoral, and systemic effects. Eight mongrel dogs (weighing 11.2 to 13.1 kilograms) were anesthetized with sodium pentobarbital (30 mg/kg) and their hearts were exposed through a left lateral thoracotomy. The hearts were removed (while still beating) and were placed in a cold physiologic salt solution (5°C). The hearts were kept in the physiological salt solution while the proximal circumflex coronary arteries from the aortic root to the anterior ventricular marginal branch were carefully dissected free from the surrounding tissue. All branch arteries along this section of the circumflex artery were ligated and cut distally. The distal portion of the circumflex artery was cut by the anterior ventricular marginal branch and the proximal portion including part of the aortic root was also cut. The above procedure required between 30 to 45 minutes to remove the first 3 to 4 cm of the proximal circumflex artery. After removal, four arteries were placed in a physiological salt solution stored in a refrigerator overnight and studied the next day. The remaining arteries were immediately attached to the perfusion apparatus.

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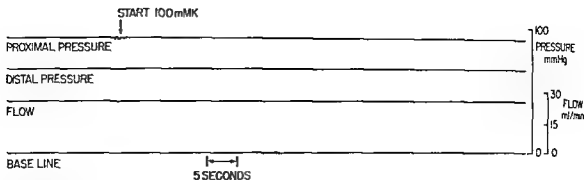


Fig 2 Typical stenotic hemodynamic response to coronary artery vasoconstriction with an external circumferential snare

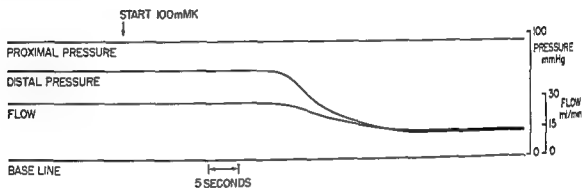


Fig 3 Typical stenotic hemodynamic response to coronary artery vasoconstriction with an intraluminal obstruction

arterial bath solution was drained and was refilled with the 1.5 mM potassium chloride physiologic salt solution.

Next, in the presence of an external constrictor, the hemodynamic response to arterial vasoconstriction was examined. External constriction was achieved by a circumferential snare. The snare consisted of a 1.0 silk suture passed around the artery through the polyethylene 160 tubing and attached to a machinist's micrometer. This is a commonly used technique to achieve arterial stenosis.¹ The artery was perfused with 1.5 mM potassium chloride physiologic salt solution and the snare was tightened to create a pressure gradient across the stenosis. The variables were recorded for 10 minutes to verify stability. The perfusate was switched to the 100 mM potassium chloride salt solution and the variables were recorded for 5 minutes. The artery was reperfed with the 1.5 mM potassium chloride physiologic salt solution, the bath solution was drained and refilled with the 1.5 mM potassium chloride physiologic salt solution. The above procedure was repeated two times on each artery studied.

Finally, the response to arterial vasoconstriction

in the presence of internal obstruction was examined. Internal obstruction (Fig 1b) was achieved by a 3F Fogarty balloon catheter. The artery was perfused with the 1.5 mM potassium chloride physiologic salt solution and the balloon was inflated to create a pressure gradient across the artery. Note that the maximum arterial diameter was determined by the perfusion pressure. Therefore, the balloon did not and could not have created a bulge in the artery while still allowing flow through the artery. The Fogarty balloon catheter was inflated with an acrylic solution (which solidified within 1/2 hour (JB-4 Polysciences, Inc)). The acrylic solution insured a fixed stable intraluminal obstruction. The variables were recorded for 30 minutes to verify stability and to allow the acrylic solution to solidify. The perfusate was switched to the 100 mM potassium chloride salt solution and the variables were recorded for five minutes. Provided there was still a perfusion flow, the artery was reperfed with the 1.5 mM potassium chloride physiologic salt solution, the bath solution was drained and refilled with the 1.5 mM potassium chloride physiologic salt solution. When the intraluminal obstruction plus the 100 mM potassium chloride

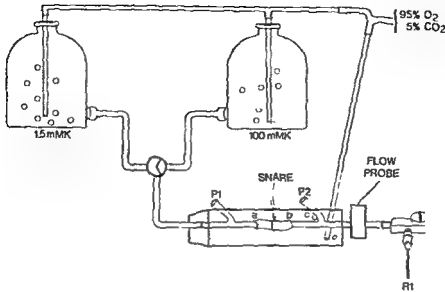


Fig 1a Diagram of in vitro constant pressure perfusion system. External constriction. P_1 = proximal pressure, P_2 = distal pressure, a = proximal and b = distal points of attachment for artery. P_1 ~ 20 gauge Longwell needle.

ratus and were studied. There was no difference in response between the arteries studied after overnight storage in refrigerated physiologic salt solution and those used immediately.

The perfusion apparatus (Fig 1a) consisted of two pressure reservoirs, an arterial bath, and fixed distal resistance. One reservoir contained a 15 mM physiologic salt solution (composition in millimoles per liter: 122.0 NaCl, 25.0 NaHCO₃, 1.2 NaH₂PO₄, 1.2 MgSO₄, 1.5 KCl, 2.5 CaCl₂, and 10 pyruvic acid, pH = 7.42) while the other reservoir contained a 100 mM solution (composition in millimoles per liter: 24 NaCl, 25 NaHCO₃, 1.2 NaH₂PO₄, 1.2 MgSO₄, 100 KCl, 2.5 CaCl₂, 10 pyruvic acid, pH = 7.42). The arterial bath was filled with the 15 mM physiologic salt solution. All solutions were maintained at 37° C and were equilibrated with a gaseous mixture of 95% O₂, 5% CO₂. The distal resistance was a 20 gauge Longwell needle. Proximal and distal pressures were measured with pressure transducers (Statham). Perfusion flow was measured with an extracorporeal flow probe (Biotronix). This flow probe was calibrated by a timed collection in a graduated cylinder. The data were recorded on a multichannel recorder (Electronics for Medicine model DR-8).

The artery was placed in the bath solution attached to point a and b (Fig 1a) and stretched to its in vivo length. The reservoir pressure was

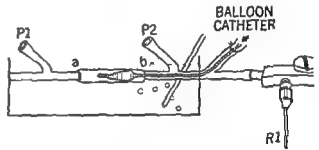


Fig 1b Diagram of in vitro constant pressure perfusion system. Internal obstruction. Abbreviations and symbols same as in Fig 1a.

applied to the arterial segment and the artery was allowed to stabilize for two hours. The reservoir pressure and the arterial length were kept constant throughout the experiment.

Prior to creating the stenosis the hemodynamic response to arterial vasoconstriction was examined. The distal stopcock was opened and the perfusate was allowed to flow through the artery. The variables were recorded while the artery was perfused with the 15 mM physiologic salt solution. After five minutes the perfusate was then switched to the 100 mM salt solution and the variables were recorded. Changing from a 15 mM solution to a 100 mM solution causes consistent coronary artery vasoconstriction. After five minutes the artery was reperfused with the 15 mM physiologic salt solution and the

Table I Hemodynamic effects of coronary artery vasoconstriction

| | Proximal pressure (mm Hg) | Distal pressure (mm Hg) | Flow (ml/min) | Stenotic resistance (mm Hg/ml min) | Distal resistance (mm Hg/ml min) | Proximal diameter (cm) | Distal diameter (cm) |
|------------------------------|---------------------------|-------------------------|---------------|------------------------------------|----------------------------------|------------------------|----------------------|
| No constriction | | | | | | | |
| 15 mM K | 94.7 | 91.1 | 31.1 | — | 2.94 | 3.1 | — |
| | ± 1.2 | ± 1.3 | ± 1.0 | | ± 0.08 | ± 0.3 | |
| 100 mM K | 94.5 | 90.5 | 30.1 | — | 3.0 | 3.0 | — |
| | ± 1.6 | ± 1.8 | ± 1.4 | | ± 0.13 | ± 0.3 | |
| External constriction | | | | | | | |
| 15 mM K | 93.0 | 68.4 | 25.9 | 1.07 | 2.66 | 3.1 | .99 |
| | ± 1.8 | ± 4.9 | ± 2.0 | ± 0.25 | ± 0.07 | ± 0.1 | -.01 |
| 100 mM K | 93.5 | 68.0 | 25.5 | 1.13 | 2.68 | 3.1 | .99 |
| | ± 2.0 | ± 5.3 | ± 2.0 | ± 0.28 | ± 0.09 | ± 0.1 | +0.1 |
| Internal obstruction | | | | | | | |
| 15 mM K | 94.9 | 69.3 | 27.1 | 1.12 | 2.57 | 3.2 | .99 |
| | ± 0.9 | ± 4.9 | ± 1.7 | ± 0.29 | ± 0.07 | ± 0.1 | -.01 |
| 100 mM K | 94.9 | 18.2* | 11.8 | 10.6* | 1.46 | 3.1 | .99 |
| | ± 1.0 | ± 5.6 | ± 2.0 | ± 2.86 | ± 0.2 | ± 0.1 | 0* |

All data values are mean ± standard error of mean

* P < 0.01 compared to 15 mM K response by Student's t test

vasodilation on pressure and flow in a stenosis that was created with the intraluminal balloon. After obtaining the response described in Fig 3 the perfusate was switched back to a 15 mM K physiologic salt solution. This reperfusion resulted in a return of flow and an increase in distal pressure, thus allowing the initial stenotic hemodynamics to be restored. It should be pointed out that if the flow reduction caused by arterial vasoconstriction was severe (flow less than 1 ml/minute) reperfusion was ineffective in reestablishing the initial conditions because the 15 mM K solution could not reach the stenotic site. In these experiments nitroglycerin (0.4 mg) was added to the arterial bath solution. This reestablished the initial stenotic hemodynamics.

Table I summarizes the results from the eight coronary arteries studied. Table I is based upon eight observations with no constriction, 16 observations with external constriction, and 24 observations with an internal obstruction. The diameter data are from two experiments. Prior to the creation of an arterial stenosis, vasoconstriction had no significant effect on the measured and calculated variables. Similarly, with arterial stenosis produced by an external circumferential snare, arterial vasoconstriction had no significant effect on the measured and calculated variables. In striking contrast, with stenosis produced by an intraluminal balloon catheter, arterial vasocon-

striction caused significant hemodynamic changes. Distal pressure, flow, and distal diameter decreased, and the stenotic resistance increased markedly. Thus, internal obstruction potentiated the effects of arterial vasoconstriction, causing significant hemodynamic changes.

Discussion

This is the first experimental model where a reduction in flow through the coronary artery has been achieved by proximal coronary artery vasoconstriction. Other animal experiments have shown a coronary flow reduction caused by vasoconstriction along the entire coronary vasculature. However, this is the only animal model where proximal coronary artery constriction alone (vasoconstriction along the first 3 cm of the coronary artery) has been able to reduce flow through the vessel. In light of the current clinical interest in coronary artery spasm, where the major pathophysiologic mechanism appears to be an abnormal contraction in the proximal coronary artery, this animal model is an important first step in understanding some of the hemodynamics of coronary artery spasm.

This study demonstrates the striking hemodynamic effect of arterial vasoconstriction when a partial luminal obstruction is present. Neither the arterial vasoconstriction alone in the normal vessel nor the stenosis alone caused a significant

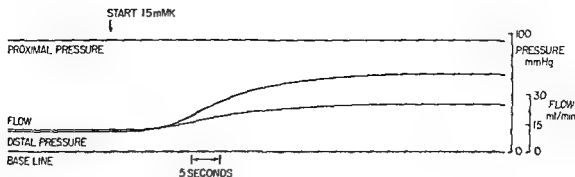


Fig 4 Typical stenotic hemodynamic response to coronary artery vasodilation with an intraluminal obstruction

caused the perfusion flow to cease nitroglycerin (0.4 mg) was added to the bath. This always caused a relaxation of the artery and reestablished the normal perfusion flow. The above procedure except for inflating the balloon was repeated three times on each artery studied.

In the last two experiments the diameters of the circumflex artery proximal and distal to the stenotic site were measured with a calibrated eyepiece (magnification 7X). The diameters were measured just before and during the perfusion with the 100 mM potassium salt solution.

The stenotic resistance was calculated as the pressure gradient across the stenosis divided by the flow through the stenosis. The pressure gradient being the proximal pressure minus the distal pressure. The distal resistance was calculated as the distal pressure divided by the flow. The stenotic and distal resistances were only calculated when the flow was greater than 1.0 ml/minute. In each data group the mean and the standard error of the mean were determined for the proximal pressure, distal pressure, flow, stenotic resistance and distal resistance. Statistical significance was determined by comparing the 15 mM potassium response to the 100 mM potassium response by the Student's *t* test.

Results

Fig 2 shows the effects of coronary artery vasoconstriction on pressure and flow in the artery. An initial stenosis was created with an external circumferential snare. With a 15 mM potassium salt solution perfusing the artery the initial stenosis was established and allowed to stabilize for ten minutes. The perfusate was switched to a 100 mM potassium salt solution indicated by the arrow in Fig 2. The 100 mM potassium solution was

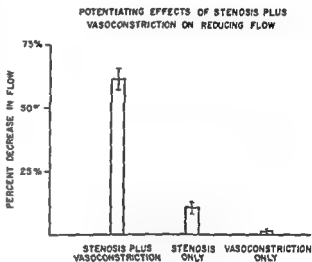


Fig 5 Diagram showing synergistic effects of stenosis and vasoconstriction on reducing flow

used to induce arterial vasoconstriction. As can be seen in Fig 2 maximum arterial vasoconstriction caused no observable effects on the flow through and the pressure across the stenosis produced by an external circumferential snare.

Fig 3 shows the effects of coronary artery vasoconstriction on pressure and flow in a stenosis that was created with an intraluminal Fogarty balloon catheter. With a 15 mM potassium salt solution perfusing the artery the initial stenosis was established and was allowed to stabilize for 30 minutes. The perfusate was then switched to a 100 mM potassium salt solution. As can be seen in Fig 3 arterial vasoconstriction severely reduced the flow through and increased the pressure across the stenosis. Thus stenoses created by internal obstruction were extremely sensitive to arterial vasoconstriction.

Fig 4 shows the effects of coronary artery

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flow change but when present together they act synergistically to produce a marked reduction in the arterial lumen a large pressure gradient and a significant reduction of flow (see Fig 3)

Conversely with partial stenosis created by a circumferential snare subsequent arterial vasoconstriction had little effect on stenotic hemodynamics. The initial stenotic resistance flow and distal pressure (see Table I) were almost identical for stenoses created by either an external snare or by an intraluminal obstruction. Yet with external snare arterial vasoconstriction was ineffective. Conceivably the external snare shortened the circumferential vessel fibers to a maximal degree so that no further shortening was possible by vasoconstriction. This observation may be relevant to the clinical situation where although two patients may have a similar degree of stenosis only one patient will exhibit coronary artery spasm.

With the internal obstruction arterial vasoconstriction could have increased the hemodynamic severity of the stenosis by a slight reduction in the vessel radius at the stenotic site. In an otherwise normal vessel a 5% reduction in radius would cause approximately a 10% reduction in vessel area. With an initial stenosis of 85 to 90% a 5% reduction in vessel radius can occlude the artery. Also the Bernoulli Principle might increase the effectiveness of the vasoconstriction. According to Bernoulli's equation the pressure by the stenosis is reduced. This stenotic pressure decrease would allow the vessel to constrict even further the lower the intraluminal pressure the greater the resulting vessel radius decrease for the same vasoconstriction stimulus.

There is increasing evidence in man that some episodes of angina pectoris may be caused by arterial spasm superimposed on the atherosclerotic stenosis of a major coronary artery. In these patients coronary artery spasm can be induced by intravenous ergonovine maleate or by hyperventilation combined with tris buffer infusion and can be relieved by nitroglycerin. Coronary angiograms have shown a decrease in vessel diameter or actual closure of the vessel during angina attacks in some patients. Nitroglycerin caused these vessels to dilate. These clinical studies suggest that angina pectoris and myocardial infarction are in part associated with dynamic spasm becoming additive to fixed lesions of the coronary arteries in some patients.

Indeed Maseri and co workers have used post mortem studies to demonstrate that areas of atherosclerotic stenosis often contain a wall segment which is normal and apparently able to contract. In this study stenosis created by an intraluminal balloon catheter exhibited characteristics similar to the clinical lesion the arterial wall is able to contract arterial vasoconstriction increased stenotic severity and dilation decreased stenotic severity. We believe that this type of response is a reasonable model for at least some of the stenotic lesions found in coronary artery disease.

In our experiments if the flow reduction after arterial vasoconstriction was severe then reperfusion with the 1.5 mM K physiologic salt solution was ineffective in relieving the spasm possibly because the 1.5 mM K solution never reached the stenotic site. If arterial spasm in man resulted in temporary total occlusion with absence of flow the vasoconstriction may become irreversible because removal of the vasoconstricting stimulus if it was blood borne would be impossible.

Summary

In summary we have examined the response to arterial vasoconstriction in an in vitro coronary artery preparation. Without a preexisting stenosis arterial vasoconstriction had minimal hemodynamic effects. Similarly with a stenosis created by a circumferential snare arterial vasoconstriction had minimal hemodynamic effects. In striking contrast with a stenosis created by intraluminal obstruction arterial vasoconstriction dramatically increased the hemodynamic severity of the stenosis. The use of an intraluminal obstruction provides a useful animal model for examining hemodynamics in coronary artery disease and has provided some insight into the effects of vasoconstriction on coronary artery hemodynamics. Obviously this is an experimental study and care must be taken in extrapolating these results to diseased human coronary arteries.

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Case reports

Right ventricular endomyocardial fibrosis simulating Ebstein's anomaly

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Clinical features and the usual laboratory data as well as cardiac catheterization findings may fail to differentiate right ventricular endomyocardial fibrosis (RVEF) from Ebstein's anomaly.

Since RVEF is correctable by surgery, at least potentially differentiation of these cases from Ebstein's anomaly is important and the latter also may require surgical intervention.

Accurate bedside diagnosis of RVEF is some times possible however tricuspid regurgitation occasionally associated with a tricuspid diastolic flow may be confused with rheumatic heart disease.

This report is concerned with a case of RVEF which was operated on with a preoperative diagnosis of Ebstein's anomaly.

Case History

A 20 year-old man was admitted in January 1975 with six year history of exertional dyspnea, progressive swelling of the face and abdomen, slight bilateral ankle edema with small varicose veins and moderate mucocutaneous cyanosis.

There was neither history of rheumatic fever during childhood nor cyanosis at birth. Conjunctivae and oral mucosa were congested, jugular veins were engorged and the top of the venous column was seen at mandibular angle at 45 degree trunk elevation without prominent pulsation. Pulses were of low volume and blood pressure was 100/70 mm Hg. The patient was afebrile, Kussmaul's sign and paradoxical pulse were absent.

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The precordium was quiet. The first heart sound was widely split with very prominent second component. A soft pansystolic murmur was usually heard at the patient's first physical examination at the right lower sternal border which was accentuated by inspiration. At his second admission in 1976 when his congestive heart failure was severe this murmur could hardly be heard without any change in inspiration. Right ventricular gallop was present at both admissions. A and P waves physiologically split and were normal in intensity.

A few bilateral basal crepitant rales were present initially which cleared soon following digoxin and diuretic therapy. A moderate amount of ascites was present. The liver was enlarged 4 cm below the right costal margin.

Hepatic systolic pulsation which was present at his first admission in 1975 was not felt at the second admission and it was thought that the liver was slightly smaller.

Slight pitting edema and many small varicose veins were observed mostly around the ankles. Moderate clubbing was present.

Electrocardiogram and chest roentgenogram. The electrocardiogram showed atrial fibrillation and a pattern of incomplete right bundle branch block (RBBB) (Fig. 1). A chest x-ray revealed an enlarged balloon shaped heart with a very prominent right atrium and a narrow vascular pedicle. The enormous cardiac shadow contrasted with oligemia of the lung fields (Fig. 2).

Echocardiogram. The first echocardiogram was interpreted as simultaneous tricuspid and mitral valve echograms. Two leaflets of the tricuspid valve could be seen during the entire cardiac cycle simulating a pattern of tricuspid stenosis. The time difference between the mitral and tricuspid closure was too long, almost half a cardiac cycle. Scanning from the aorta to the mitral area revealed normal aorto mitral continuity and the anterior wall of the aorta was in continuation with what we thought was the tricuspid valve (Figs. 3 and 4).

Catheterization data and intracardiac electrocardiogram. Catheter manipulation did not induce significant arrhythmias. Atrial septal defect or patent foramen ovale was not found. Entering the right ventricle and pulmonary artery, was not easy. Leftward displacement of the tricuspid valve was noted during angiography and pressure curve recording (Fig. 5). Arterial oxygen saturation was low (82%). Mean right atrial pressure was high (24 mm Hg). Right ventricular

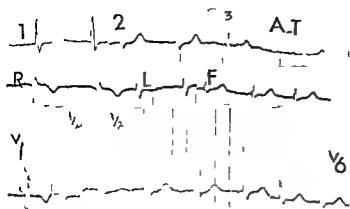


Fig 1 Atrial fibrillation and a pattern of incomplete right bundle branch block are shown in this ECG tracing

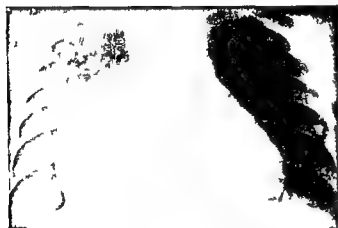


Fig 2 A chest x ray shows the enlarged balloon shaped heart with a narrow pedicle and a prominent right atrium

astolic pressure was 40 mm Hg with a high end diastolic pressure of 24 mm Hg. The right ventricular pressure curve had a dip and plateau pattern (Fig 6). Attempts to record a His bundle electrocardiogram failed. The simultaneous pressure and intracardiac electrogram was suggestive of Ebstein's anomaly (Fig 7). Pressing the electrode catheter tip against the endocardium produced marked ST segment elevation (Fig 8).

Operative and pathologic findings The heart was quite enlarged mostly due to the huge right atrium and lacked the typical rocking motion seen in patients with Ebstein's anomaly. There was no atrial septal defect or patent foramen ovale. The anterior leaflet of the tricuspid valve was wide and floppy, spared from extensive shrinkage, thickness and distortion but the posterior and septal leaflets had downward displacement due to the traction by fibrotic tissue. The entire RV cavity as well as the outflow tract was covered by a thick dense layer of fibrosis. During resection of the dense right ventricular fibrotic layer the interventricular septum was ruptured and repaired. The tricuspid valve was replaced by a porcine prosthetic valve. The patient did not do well after the operation and died because of low cardiac output syndrome mostly due to intractable right-sided failure. At autopsy the left side of the heart also was highly involved (Fig 9).

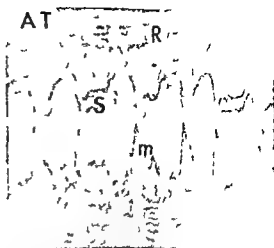


Fig 3 Mitral echogram of patient A.T. showing marked paradoxical septal motion

Comments

The incidence of pure right sided endomyocardial fibrosis is not clearly known and has been reported in different articles³ in 10% to about 50% of patients suffering from endomyocardial fibrosis.

On the right side the process may be more massive than in the left ventricle and may obliterate most of the right ventricle but it usually spares the infundibulum and pulmonary valve although the infundibulum was involved in our case.

Clinical consideration When endomyocardial fibrosis involves the papillary muscle, chords and leaflets of the tricuspid valve, tricuspid incompetence is common, often with a huge aneurysmal dilatation of the right atrium.

Right sided endomyocardial fibrosis has a slowly progressive course leading to right sided congestive heart failure in contrast to left sided or the combined form of the disease which rapidly leads to a fatal outcome. The onset of symptoms is quite insidious causing effort intolerance secondary to low cardiac output, mild cyanosis, peripheral edema, hepatomegaly and ascites. Small varicosities may be seen over the legs mostly around the ankles due to long standing high venous pressure.

The following clinical findings which were present in our patient are classically mentioned in Ebstein's anomaly⁶.

1. An unusual facial coloration is occasionally present resulting in a red cheeked or violaceous appearance.

Case reports

Right ventricular endomyocardial fibrosis simulating Ebstein's anomaly

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Clinical features and the usual laboratory data as well as cardiac catheterization findings may fail to differentiate right ventricular endomyocardial fibrosis (RVEF) from Ebstein's anomaly.

Since RVEF is correctable by surgery at least potentially differentiation of these cases from Ebstein's anomaly is important and the latter also may require surgical intervention.

Accurate bedside diagnosis of RVEF is sometimes possible; however, tricuspid regurgitation occasionally associated with a tricuspid diastolic flow may be confused with rheumatic heart disease.

This report is concerned with a case of RVEF which was operated on with a preoperative diagnosis of Ebstein's anomaly.

Case History

A 20-year-old man was admitted in January 1975 with a six-year history of exertional dyspnea, progressive swelling of the face and abdomen, slight bilateral ankle edema with small varicose veins and moderate mucocutaneous cyanosis.

There was neither history of rheumatic fever during childhood nor cyanosis at birth. Conjunctivae and oral mucosa were congested; jugular veins were engorged and the top of the venous column was seen at a mandibular angle at 45 degree trunk elevation without prominent pulsation. Pulses were of low volume and blood pressure was 100/70 mm Hg. The patient was afebrile. Kussmaul's sign and paradoxical pulse were absent.

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The precordium was quiet. The first heart sound was widely split with very prominent second component. A soft pansystolic murmur was initially heard at the patient's first physical examination at the right lower sternal border which was accentuated by inspiration. At his second admission in 1977 when his congestive heart failure was severe this murmur could hardly be heard without any change in inspiration. Right ventricular gallop was present at both admissions. A and P waves were physiologically split and were normal in intensity.

A few bilateral basal crepitant rales were present initially which cleared soon following digoxin and diuretic therapy. A moderate amount of ascites was present. The liver was enlarged 4 cm below the right costal margin.

Hepatic systolic pulsation which was present at his first admission in 1975 was not felt at the second admission and it was thought that the liver was slightly smaller.

Slight pitting edema and many small varicose veins were observed mostly around the ankles. Moderate clubbing was present.

Electrocardiogram and chest roentgenogram. The electrocardiogram showed atrial fibrillation and a pattern of incomplete right bundle branch block (RBBB) (Fig. 1). A chest x-ray revealed an enlarged balloon-shaped heart with a very prominent right atrium and a narrow vascular pedicle. The enormous cardiac shadow contrasted with oligemia of the lung fields (Fig. 2).

Echocardiogram. The first echocardiogram was interpreted as simultaneous tricuspid and mitral valve echograms. Two leaflets of the tricuspid valve could be seen during the entire cardiac cycle simulating a pattern of tricuspid stenosis. The time difference between the mitral and tricuspid closure was too long, almost half a cardiac cycle. Scanning from the aorta to the mitral area revealed normal aorto-mitral continuity, and the anterior wall of the aorta was in continuation with what we thought was the tricuspid valve (Figs. 3 and 4).

Catheterization data and intracardiac electrocardiogram. Catheter manipulation did not induce significant arrhythmias. Atrial septal defect or patent foramen ovale was not found. Entering the right ventricle and pulmonary artery was not easy. Leftward displacement of the tricuspid valve was noted during angiography and pressure curve recording (Fig. 5). Arterial oxygen saturation was low (87%). Mean right atrial pressure was high (23 mm. Hg). Right ventricular

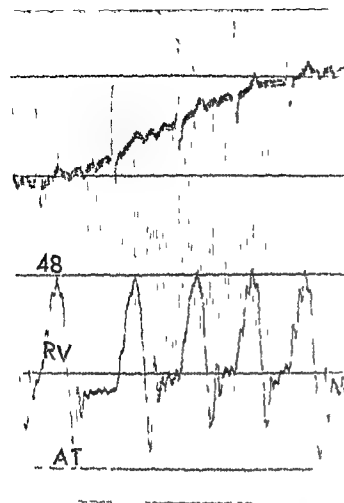


Fig 6 A right ventricular pressure curve illustrates a dip and plateau pattern and high end diastolic pressure

Conduction disturbances were seen in 19 of the 90 cases reviewed by Razner and co workers. Bundle branch block and intraventricular conduction delays were the most frequent occurrences not surprising in view of the endomyocardial thick fibrotic lesion. In endomyocardial fibrosis unlike fibroelastosis the normal layers of the endocardium are destroyed and are replaced by thick scar tissue although only one patient out of 21 patients reviewed showed the pattern of incomplete RBBB. This is in contrast to Ebstein's anomaly in which 75% to 80% of these patients have a complete or incomplete RBBB although this is considered atypical because of the low voltage and polyphasic configuration and it has no specific or diagnostic feature.

Echocardiography Simultaneous recording of the tricuspid and mitral valve echograms is not unusual in Ebstein's anomaly. Decreased tricus-

pid diastolic closure slope (E F slope) is one of the echocardiographic features of this anomaly although the amplitude of what was thought to be two leaflets of the tricuspid valve was less than mitral valve motion and this is not the case in Ebstein's malformation. According to Lundstrom¹³ an echo from the posterior or septal tricuspid leaflet is rarely recorded in Ebstein's anomaly. Delayed tricuspid closure is considered to be the most consistent echocardiographic feature of the abnormally positioned tricuspid valve but its continuation with the anterior wall of the aorta cast doubt on our previous belief and apparently this was the interventricular septum with markedly exaggerated paradoxical motion (Fig 3). Although it is said that all patients with Ebstein's malformation have type B septal motion (the septal echoes become flattened during systole instead of anterior motion in type A) five out of 19 patients reported by Lundstrom had type A septal motion. Therefore Ebstein's anomaly could not be ruled out by this finding.

Interpretation of catheterization data and electrophysiological studies

Leftward displacement of the tricuspid valve has been considered a valuable sign in Ebstein's anomaly and this was also apparent in our patient. The apex of the right ventricle (RV) was obliterated by scar tissue and the RV cavity was shrunk and contracted. This was confirmed by RV angiography, which showed the absence of the usual apical cavity initially thought to be the RV proper of Ebstein's anomaly (Fig 6).

Atrial septal defect or patent foramen ovale which was present in 14 out of 65 cases with Ebstein's anomaly, was not found.¹ In a report by Kumar and associates¹⁴ seven out of 50 patients with Ebstein's malformation developed transient tachycardia; this did not happen in our patient. Difficulty in entering the RV and pulmonary artery, low arterial O₂ saturation and high mean right atrial and RV end diastolic pressures may be encountered in both entities. The RV pressure curve had a dip and plateau pattern stimulating constrictive pericarditis but this may be seen in chronic right sided disease per se as effusion, primary pulmonary hypertension and with intracardiac tumor.¹⁵ This appearance of the fibrotic process causing an early diastolic

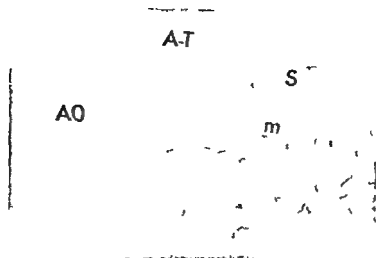


Fig 4 Echogram of the patient showing aortic mitral continuity

2 The relatively unimpressive jugular venous pulsations present because of the huge right atrium and the toneless atrialized right ventricle

3 Absence of a systolic impulse over the body of the right ventricle

4 Early systolic murmurs in Ebstein's anomaly generally do not increase during inspiration despite their tricuspid origin

In reviewing 10 patients with Ebstein's anomaly Crew and associates have found that the only constant anomaly was abnormally wide splitting of the first sound with accentuation of the delayed component. This abnormal sound was thought to be caused by delayed closure of the abnormally large anterior leaflet of the tricuspid valve. The intensity of the sound despite a hypodynamic right ventricle is of interest in relation to the mechanism of heart sounds.

According to Fontana and colleagues the systolic sound may not be a closure sound since it is present in cases with considerable tricuspid regurgitation where the leaflets may not approximate at all. The sound is probably more related to the termination of motion of the anterior leaflet which was larger than usual in our patient.

Electrocardiography In studying the electrocardiographic findings in 30 cases of endomyocardial fibrosis no specific diagnostic pattern was found except for an abnormal P wave (P mitrale or pulmonale), a low voltage QRS and nonspecific changes in T waves.

Atrial flutter or fibrillation are seen in only 2% to 5% of patients with Ebstein's anomaly while

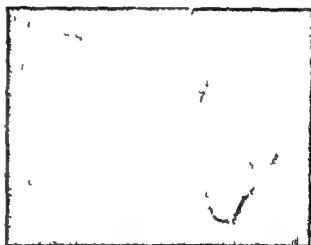


Fig 5 Right ventricular angiogram shows leftward displacement of the tricuspid valve with a dilated right atrium

six of 11 patients with endomyocardial fibrosis had this rhythm. Our patient had both atrial fibrillation and a pattern of incomplete right bundle branch block (Fig 1).

Although our patient did not have episodes of supraventricular tachyarrhythmias which are well known in Ebstein's anomaly, a high incidence of arrhythmias is reported in endocardial fibroelastosis, probably due to degenerative changes in the cells of the cardiac ganglia. We are not aware of this histologic change in endomyocardial fibrosis. The absence of supraventricular tachyarrhythmias in our patient could be due to atrial fibrillation which is rare in Ebstein's anomaly and is rather common in endomyocardial fibrosis.

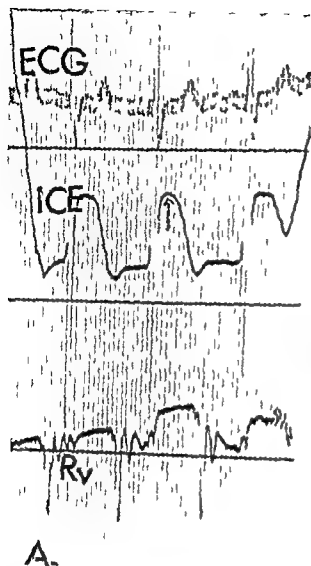


Fig 8 Intracardiac electrogram recorded while pressing the electrode catheter tip against the right ventricular endocardium damping the pressure and producing a contact potential (arrow)

retrospect was considered to be probably due to a thick layer of fibrosis covering the septal surface of the right ventricle

Conclusion

A differential diagnosis between these two rare entities which require different therapeutic approaches is important. The reported results of surgical treatment of RVEF are encouraging while in Ebstein's anomaly this is not the case and one should be more conservative in sending patients for operation. Clinical features and chest roentgenograms could be quite similar and elec-



Fig 9 At autopsy a thick layer of right ventricular endocardial fibrosis was found

trophysiologic studies may be misleading. Cineangiograms rather than rapid sequence films seem to be very reliable for this differentiation

Summary

A case of right ventricular endomyocardial fibrosis simulating Ebstein's anomaly is described. The clinical features, chest x-ray, electrocardiogram, echocardiogram, intracardiac electrogram, and the angiogram were all compatible with Ebstein's malformation. A correct diagnosis was subsequently made in the operating room. Reasons for the difficulties in the differential diagnosis of these two entities are discussed.

We wish to thank Dr Jam Shalibi for his assistance in preparation of this manuscript and Dr Harvey Feig for interpreting the echocardiogram.

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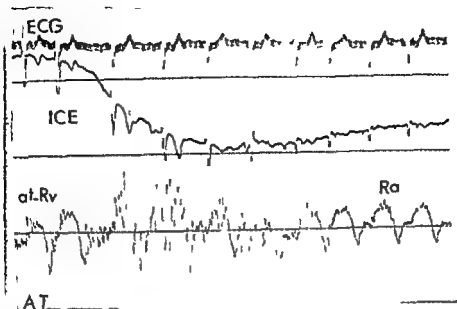


Fig 7 Simultaneous intracardiac electrogram (ICE) and pressure recording. An intracavitary potential is recorded immediately after withdrawing the catheter from the right ventricle presumably into the atrialized right ventricle (at RV).

recoil after termination of RV contraction (Fig 6). In severe RVEF the right ventricular apex is mostly obliterated and the infundibulum is dilated with tricuspid regurgitation. Pressure pulses from the pulmonary artery, the RV and the right atrium are distorted and resemble each other. This entity could be quite similar to Ebstein's anomaly when the pressure curves are identical. In our case the pressure curves were similar but not identical (Fig 7). Therefore localization of the catheter tip by pressure pulse could be inaccurate. It is known that when an electrode catheter touches the normal endocardium there will be an ST segment elevation which is called "contact potential" rather than current of injury.¹⁰ Some authors believe that this contact potential may be almost absent or minimal when the electrode touches the area which is covered by a thick layer of endocardial fibrosis. Significant ST elevation was present in our right ventricular intracardiac electrocardiogram in spite of a diffuse and thick layer of RV endomyocardial fibrosis (Fig 8). Probably by repeated catheter manipulation and positioning we could also get right ventricular pressure and ECG pattern without ST elevation. According to Sodí Pallares,¹¹ this contact potential should be recorded when the atrialized right ventricle is also touched by the

catheter tip whereas contact with the true atrial endocardium should produce elevation of the P-Q segment. Although ST segment elevation was produced in only one out of eight patients studied by Lowe and co-workers,¹² this change was clearly shown in our patient. Upon withdrawing the catheter when the pressure dropped and the pressure curve changed slightly, hand injection of dye proved that the catheter tip was out of the RV. In this position the QRS voltage decreased markedly but a ventricular pattern (rs) remained. There was no ST segment elevation (Fig 7).

Watson¹³ has mentioned many pitfalls in intracardiac electrocardiography and the reasons for having false positive and false negative diagnoses of Ebstein's malformation. It has been demonstrated that a normal intracardiac electrocardiographic and pressure relationship might be present when the catheter is withdrawn across the anterior tricuspid leaflet or true annulus at the midatrial level. When the right ventricular cavity is obliterated or contracted due to RVEF, the difference in the magnitude as well as the direction of the unbalanced electrical forces on two sides of the high ventricular septum may cause an electrode catheter to continue to record ventricular potentials after it entered the right atrium.

Failure to record His bundle deflection in

Congenital pericardial defect associated with cardiac incarceration Case report

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Futsumi Hotta
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A congenital defect of the pericardium is rare. Since Columbus reported the first case in 1559, only around a hundred cases have been found in the whole world. Though such symptoms as palpitation and exertional chest pain occasionally occur, the overwhelming majority of the patients remain asymptomatic and the defect is discovered by chance in a postmortem examination or operation.

A young child with the congenital pericardial defect who died of incarceration of the left ventricle was seen at the Tokyo Medical College Hospital. The clinical course and autopsy findings are described below.

Case report

This 4-year-old boy had been healthy since birth. In the evening of April 19, 1979, he had a fight with his 7-year-old sister over a book and accidentally struck his chest with his own fist. Chest pain started immediately after this episode which was agonizing and was accompanied by gradually increasing facial pallor. He was admitted to a nearby hospital 30 minutes after the accident. Chief findings on admission were as follows: no cyanosis, lethargic, respiration rate 44/minute, pulse rate 135/minute, blood pressure 93/66 mm Hg, body temperature 37.3°C, systolic murmur over the apex and the lower palpable for 3/4 in. Peripherical blood count showed a neutrophilia (white blood count 12,000/mm³, 70% neutrophils). ECG recording taken in the morning after admission showed a strong right axis deviation and a depression of the ST segment as well as a depression in Leads II, III and aV₁ from which we suspected the inferior wall through the apex was involved. A chest x-ray disclosed deviation of the heart to the left, abnormal

protrusion of the left third and fourth arch, and a small lung marking (Fig. 1, left).

After admission, chest pain persisted, the respiration became worse and the patient sometimes cried. His systolic blood pressure fell to 64 mm Hg. Oxygen therapy, adrenocortical hormones, cardiotonic and intravenous bicarbonate solution were used. Twelve hours after onset, the pulse was 110/minute, irregular and faint while the nail bed was cyanotic. ECG recordings taken 13 hours after onset showed that the ST segment contrary to the previous findings was depressed in Leads II, III and aV₁ and was elevated in Leads I, aV₁ and V₁ to V₆ which suggested a coronary artery disease lateral wall (Fig. 1B). The patient was referred to our hospital at 2 P.M. on April 20, 1979, at which time respiration and lethargic measurement of blood pressure was not feasible. pulse rate was 80/minute, respiration rate was 20/minute, generalized cyanosis as well as edema of the face and extremities were noted. Chest x-ray revealed more marked protrusion of the left third and fourth arch (Fig. 2, right). The patient died 20 minutes after admission, 19 hours after onset.

Gross findings at autopsy were as follows. A tumor of the apex size was observed on the left side of the heart on opening the chest, which, when the heart was removed, was found to be the left ventricular wall protruding through the pericardium created by a partial defect of the pericardium (3.5 x 4.5 cm) created by a partial defect of the pericardium. The ventricle that the left ventricle was incarcerated. The ventricle wall at the borders of the incarceration was squarish and presented a picture of a clear deep entrapment, especially the posterior wall. The incarcerated part was clearly different from the normal part in color tone. The part in which incarceration included the apex, the posterior and lateral wall and a portion of the anterior wall of the left ventricle (Fig. 3 and 4).

Besides the aforementioned abnormalities, the right side of the fluid was accumulated only in the left thoracic cavity and the liver and lung were congested.

Histopathologically, the periphery of the pericardial defect were marked by conspicuous thickening of the pericardial layer, pericardium and by an increase in collagen fibers (Fig. 4). The myocardium in the incarcerated part was markedly thickened in general and showed congestion and hemorrhage as well as necrosis here and there besides being infiltrated by inflammatory cells. Myocardial necrosis was more conspicuous in the anterior than on the posterior wall. Around the posterior part, myocardial infarction was more severe than in the healthy part (Fig. 5).

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Fig 3 Autopsy findings A Frontal aspect of the resected heart the incarcerated left ventricle is seen as a dark mass on the right side B Posterior aspect of the resected heart the incarcerated left ventricle is seen as a dark mass on the left side Distension of the coronary vessels is clear

Table 1 Reported cases of death due to cardiac incarceration in congenital pericardial defect

| Author | Nationality | Year | Age of patient | Sex | Site | Time between onset & death |
|-------------------|--------------|------|----------------|-----|----------------|----------------------------|
| 1 Boxall | — | 1887 | 28 yrs | F | Apex | 30 hr |
| 2 Sunderland | Australia | 1944 | 2 yrs | M | Left ventricle | 14 hr |
| 3 Bruning | South Africa | 1961 | ~ yrs | F | Apex | 19 hr |
| 4 Present authors | Japan | 1979 | 4 yrs | M | Left ventricle | 19 hr |

Subjective symptoms are rare with either type of the defect. In the left extensive defect, however, absence of the support for the left sided heart sometimes leads to such complaints as palpitation, sensation of throbbing heart and chest pain at the time of exertion, and the heart is frequently found to be deviated to the left on x-ray examination. The left partial defect is sometimes discovered from an abnormal shadow in the chest (protrusion of the left second arch) due to deviation of the left atrium. Very rarely the left atrium and left ventricle protrude through the partial defect, and the patient dies from incarceration. Robin and associates reported their success in life-saving surgery for incarceration of the left atrium that was discovered while performing emergency surgery for sudden shock in a 28-year-old man with the left partial pericardial defect. If a part of the left ventricle is incarcerated through the defect, the coronary artery is

compressed, with resultant myocardial infarction and death. The aforesaid accident is extremely rare and so far has been found only in three cases in the literature^{2,3} including one reported by Boxall in 1887.¹ Onset was sudden and death occurred in a relatively short time in all the cases (Table 1).

In the present case, the pericardial defect was located in the region of the left ventricle and was large enough to permit protrusion of the left ventricle, which constituted the primary factor for incarceration of the left ventricle. Histologically, the inner side of the border of the pericardial defect was thickened and a flap-like part between the outer and the inner side was covered with fat, while the outer membrane contained markedly fibrotic small vessels here and there. The above changes suggest that mechanical stress had been applied to the said tissue for a long time. The left ventricular wall showed a

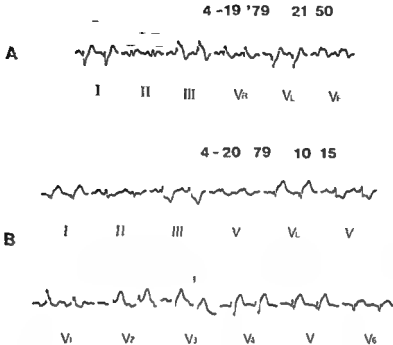


Fig 1 A ECG on admission Right axis deviation elevation of the ST segment and inversion of the T wave in Leads II III and aV B ECG recordings taken 13 hours after onset Depression of the ST segment in Leads II III and aV and elevation of the ST segment in Leads I aV and V₄ to V₆

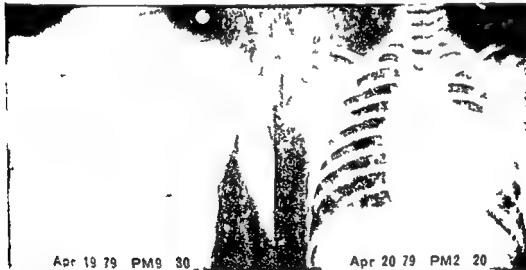


Fig 2 Chest x ray Left one hour after onset Right 13 hours after onset There is deviation of the heart shadow to the left abnormal protrusion of the third and fourth aortic arches, and intensification of the lung marking

Discussion

Congenital pericardial defect is a relatively rare congenital anomaly originating in agenesis of the pericardium and parietal pleura. According to Perna, a defect of the pericardium and pleura results if the left common cardiac vein (Cuvier's duct) atrophies early around the eighth em-

brionic week, since nutrition of the pleuropericardial membrane separating the pleural and the pericardial cavity is disturbed by such an early obliteration. Because the right Cuvier's duct remains as the superior vena cava, this anomaly is usually found on the left side. It may be extensive or partial, depending upon the size of the defect.

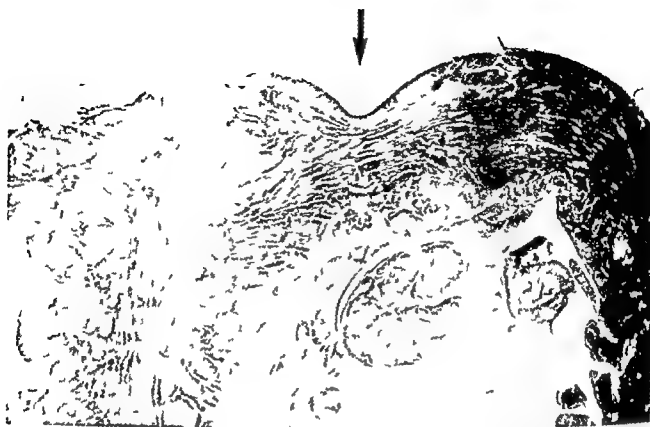


Fig 5 Histological view of the myocardium of the left ventricle. Left normal. Right the incarcerated part that shows hemorrhage and necrosis. The arrow shows the impression produced by the border of the pericardial defect.

through fixing of the heart with the use of Teflon mesh. These surgical treatments, however, must be preceded by preoperative diagnosis for which the aforesaid diagnostic procedures are useful.

Summary

1. A 4-year-old boy with the congenital partial defect of the left pericardium who presented with myocardial infarction died of incarceration of the left ventricle.

2. This is the fourth reported case of death from this anomaly in the world.

3. Because this anomaly occasionally causes sudden death, it is important to diagnose the condition while the patient is alive.

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Fig 4 Peripheries of the pericardial defect *a* shows thickening of the inner layer *b* shows marked fibrosis of the outer membrane of small vessels in the flap like portion

sion produced by a ligament on the posterior from which that part of the ventricular wall was considered to have repeatedly passed through the pericardial defect to protrude or back for a considerably long time. Application of an external force to the chest in the form of a thrust was considered to have precipitated a considerable protrusion of the ventricular wall, which ischemia of the inferior and posterior wall of the left ventricle occurred first, then its return was inhibited as the anterior wall was pushed outside in turn and congestion, edema and decrease in arterial flow ensued in that order with the resultant severe cardiac failure and death.

ECG recordings showed elevation of the ST segment in Leads II, III and aV_F immediately after admission and marked elevation of the ST segment in Leads I, aV_L and V to V₁₂ 13 hours later. The aforesaid changes in the ECG indicated that myocardial necrosis progressed from

the lateral to the anterior wall. This finding agreed with the histological findings.

In the present case a systolic murmur was heard after the occurrence of incarceration. This heart murmur seemed to have resulted from functional failure of the papillary muscle due to myocardial necrosis and subsequent mitral insufficiency. In all the previously reported cases of death from cardiac incarceration mentioned above a systolic murmur was noted.

Since sudden death occasionally occurs with the congenital pericardial defect, it is important to diagnose the condition while the patient is alive. Diagnosis is generally made by chest x-ray, ECG, echocardiography and artificial pneumothorax. A jugular phlebogram is helpful as a safe test causing little pain.

The treatment of the congenital pericardial defect consists of closure of the defect by direct suture or fixing of the heart to the diaphragm and colleagues reported that they obtained good results

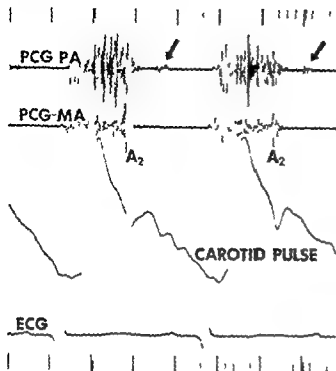


Fig 1 Phonocardiogram of pulmonary area (PCG PA) and mitral area (PCG MA). A harsh systolic murmur and a diastolic sound (arrows) were recorded. The murmur continued beyond the aortic component of the second heart sound (A₂) and the sound was separated approximately 150 msec from A. Time intervals equal 40 msec.

the tricuspid orifice to the right atrium. Pulmonary regurgitation was noted. During lephase the left side of the heart was normal. There was no intracardiac shunt.

Operative findings. Surgery performed with the diagnosis of right ventricular tumor. A palpable thrill during systole was present over the right ventricular outflow tract. A transverse right outflow tract incision was made exposing the pedunculated intracavitary tumor. The tumor was 6 × 3 × 2.5 cm in size and 27 g in weight (Fig 6). It was easily delivered from the pulmonary artery through the pulmonary valve which appeared to be normal. The attachment was entirely excised including the full thickness of the anterior right ventricular wall. The pathological diagnosis was myxoma. The patient had an uneventful recovery.

In a postoperative echophonocardiogram the tumor echoes were no longer visible in the right ventricular outflow tract. The right ventricular dimension was still increased, but a normal pulmonary valve was recorded. No adventitious systolic or diastolic sounds were recorded.

Angiographic analysis. In order to investigate the relationship between the motion of the tumor and the diastolic sound we traced frame by frame the configuration of the tumor provided by cineangiography (Fig 7). In mid-diastole the tumor fell back into the entrance and reached its most anterior and inferior position where it could be seen to strike the right entrance in the lateral angiographic views (arrows in Fig 7). In pressure when the right ventricle remained dilated atrial pressure forced the tumor upwards, toward

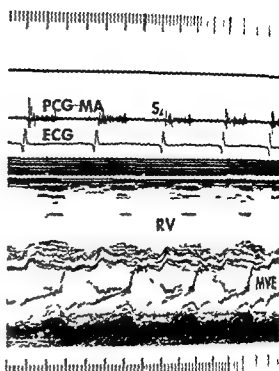


Fig 2 Echophonocardiogram showing the distention of the right ventricle (RV). The interventricular septum was abnormal in that it moves anteriorly in early systole. MVE = mitral valve echogram. Vertical distance between dots is 1 cm. S₄ = fourth heart sound.

the pulmonary valve and with the subsequent ventricular contraction part of the tumor was propelled through the valve retaining this advanced position throughout systole. The pulmonary valve could not be seen clearly throughout the cardiac cycle but in diastole the tumor mass was clearly located below the valve.

Discussion

Myxoma of the right ventricle is extremely rare compared to its occurrence in the right or left atrium. We could find only 33 reported cases in the literature.¹⁻⁴ These consisted of 18 males and 15 females with ages of 2 months to 60 years averaging 26.8 years. Clinical findings as well as physical manifestations are mainly dependent on the position and size of the tumor within the right ventricle. Most myxomas are movable or pedunculated and sometimes have a long stalk except for one adult case⁵ and two infant cases⁶ in which the tumor cells infiltrated the myocardium. Right ventricular myxomas usually originate in the free wall or in the interventricular septum and in some cases in the tricuspid valve⁷, the pulmonary ring⁸ or the val-

Right ventricular myxoma Case report and review of phonocardiographic and auscultatory manifestations

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Tumors of the right ventricle are extremely uncommon. We recently observed a patient with a right ventricular myxoma whose physical findings included a peculiar sound in mid diastole. The purpose of this case report is to describe the pathogenesis of this vibration a tumor plop as determined by combined echo and phonocardiographic studies supplemented by cineangiography. Previously reported cases are reviewed with special reference to phonocardiographic and auscultatory findings.

Case Report

A 78-year old man was admitted to North Carolina Memorial Hospital for evaluation of a heart murmur. The patient had been in good health until two years previously. At that time he noticed a "pressure" feeling in his chest when he lifted moderately heavy objects or climbed stairs. He also noted palpitations and shortness of breath. He had no diaphoresis, nausea or pain. He had a history of having been athletically inclined and instituted a program of weight control and physical conditioning in order to overcome his symptoms. He lost 70 pounds from 190 to 120 but was unable to diminish the palpitations and dyspnea. In June 1979 when he was jogging as he had done on many occasions he had a sudden dizziness followed by syncope of brief duration. This was accompanied by palpitation and a flushed feeling with dyspnea. He consulted a local physician who noticed a heart murmur and referred him to our hospital. The patient had no history of

rheumatic fever frequent respiratory infections, or cyanosis. Past and family history were unremarkable.

On physical examination the patient was of athletic build. His blood pressure was 121/93 mm. Hg pulse 76/minute and regular respiration 16/minute and temperature was 98.9 F. The jugular pulse showed a prominent "a" wave. Carotid arterial pulse had a normal upstroke without thrill. There was no heave or thrust of left or right sided ventricular enlargement. The first heart sound was normal. There was a harsh, grade 4 systolic murmur with a thrill in the second intercostal space. The murmur did not vary in intensity with respiration. An additional sound was audible in mid-diastole.

His chest roentgenogram showed mild cardiomegaly with out specific right ventricular enlargement or poststenotic dilatation of the pulmonary artery. The pulmonary vascular pattern appeared normal. The ECG revealed normal sinus rhythm and relatively prominent R waves with ST T abnormalities in Leads V₁ and V₂ suggestive of right ventricular strain. The phonocardiograms (Figs 1 and 2) confirmed the auscultatory findings and in addition demonstrated an atrial sound (S) of low intensity. In the second left intercostal space a diastolic sound was recorded (arrow in Fig 1) 150 msec. after A.

A conventional echocardiogram with transducer directed across the interventricular septum showed a dilated right ventricle (Fig 2). With the transducer angulated posteriorly and superiorly in the optimal direction for visualization of the pulmonary valve a dense mass was seen moving posteriorly with ventricular systole and anteriorly in diastole (T in Figs 3 and 4). Combined echophonocardiography showed that the point of apparent contact of this mass with the anterior wall of the right ventricle coincided with the first vibration of the diastolic sound noted above (Fig 4).

Right heart catheterization showed a mean right atrial pressure of 7 mm Hg right ventricular pressure of 100/10 mm Hg and pulmonary pressure of 15/7 mm Hg. The right ventriculogram demonstrated a dilated right ventricle. A large well circumscribed lobulated filling defect was noted in the outflow tract of the right ventricle prolapsing partially through the pulmonary valve with each contraction (Fig 5). The tumor was not attached to the pulmonary valve and did not appear to involve the tricuspid valve nor herniate through

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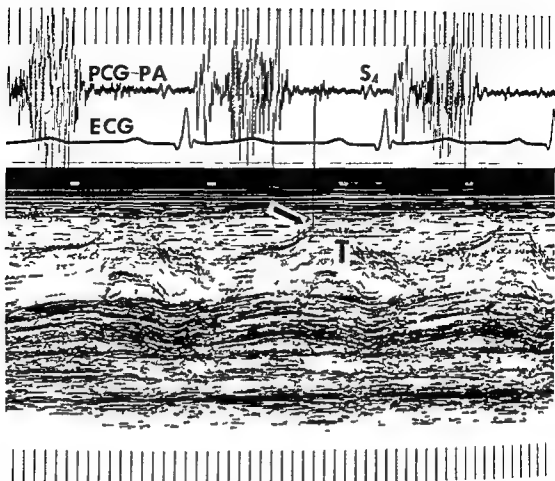


Fig 4 A high speed recording (100 mm./sec) of echophonocardiogram showing the relationship between the tumor motion and diastolic sound. In mid-diastole the tumor (T) is observed to strike the right ventricular wall (arrow) and to induce diastolic vibrations. With atrial contraction preceding ventricular ejection the tumor moved posteriorly. This probably reflects the reverse pressure gradient across the tumor in presystole as demonstrated by catheterization.

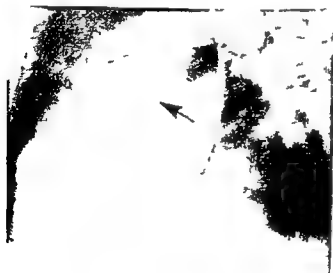


Fig 5 Lateral view of cineangiogram demonstrating the mass in the right ventricular outflow tract (arrow).

loud.^{1,22} An ejection sound was present in six cases.^{13, 20, 21, 24} However, none of the reported cases had pulmonary valvular stenosis. An opening snap was heard in one case with obstruction of the tricuspid orifice.²²

The pulmonic component of the second heart sound (P_2) and the diastolic sound or murmur are noteworthy, but were not mentioned in detail in most of the reports. S_2 in cases with pulmonary obstruction was variable—widely split and accentuated,² narrowly split, or normal.¹

Diastolic murmurs were described in 11 cases. There were three cases with tricuspid rumble due to tricuspid obstruction or regurgitation mentioned before, and four with pulmonary regurgitation.^{1, 23, 24} Two cases with pulmonary regurgitation had a perforated pulmonary valve.^{23, 24} In another case surgical replacement of the valve was performed.¹

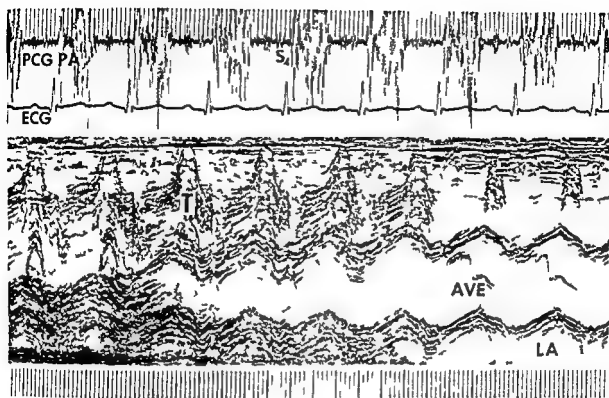


Fig 3 Scanning echocardiogram from the right ventricular outflow tract to the aortic valve (A/E). The dense echo of the tumor (T) is noted to move forward and backward with each heart beat in the outflow tract. LA = left atrium.

They tend to extend toward the right ventricular outflow tract or even prolapse through the pulmonary valve along with the blood flow in systole. Therefore typical cases present clinical findings consistent with pulmonary stenosis—symptoms of dyspnea and syncope with ejection systolic murmurs. Some cases with atypical findings have however been reported. In a rare instance there have been no symptoms. In others there have been heart failure without pulmonary obstruction,^{1, 23} endocarditis involving the pulmonary valve,^{14, 23, 24} atrial septal defect,⁴ pulmonary embolism,² bronchitis,⁶ and hemoptysis.¹ The duration of symptoms and clinical signs mentioned above varied from five weeks to 14 years.¹ There are also familial^{16, 24, 25} or recurrent cases,^{1, 2} reported.

In our review of 33 cases there were only two patients without a systolic murmur,² one of whom had an outflow obstruction gradient of 40 mm Hg.²³ Systolic murmurs in the reported cases were initially attributed to pulmonary stenosis and only retrospectively explained by the tumor

in 24 cases including three with an associated murmur of secondary tricuspid stenosis²¹ or regurgitation.² The intensity of these murmurs was variable from 2 to 6, the louder ones being associated with a palpable thrill at the upper left sternal border. The pressure gradient across the tumor was from 8 to 94 mm Hg and averaged 51.8 mm Hg. In one case in which the tumor filled the whole right ventricle and for scratchy sounds were noted.¹⁵ The intensity of the murmur varied with the positional change of the body,¹ or from one day to another.^{4, 12} The effect of respiration on the intensity of the systolic murmur was inconsistent, the murmur being decreased,²⁵ abolished,¹² intensified,²⁵ or not changed.^{12, 25} with inspiration. Pan- or holosystolic murmurs were present in four cases.^{8, 9, 13} one of which had an annuloplasty of the tricuspid valve. Thus the systolic murmur itself lacked specificity as a diagnostic sign for right ventricular myxoma.

The first heart sound (S₁) was unremarkable in all except two patients in whom it was unusually

sents tumor plops. It is unknown how often this diastolic vibration occurs in right ventricular myxoma. There is a possibility that it is missed or interpreted as delayed P₂ or diastolic murmur unless a phonocardiogram preferably in conjunction with an echocardiogram is carefully recorded. We believe its presence would be helpful in making the diagnosis just as with the tumor plop of left atrial myxoma which is due to antegrade movement of the tumor in diastole. In conclusion a diastolic sound or short vibration which occurs 130 to 160 msec after A₂, should be borne in mind as one of the auscultatory findings of right ventricular myxoma in a situation in which pulmonary stenosis is suspected.

Summary

Tumors in the right ventricle are extremely rare. This report concerns the pathogenesis of physical signs resulting from a right ventricular myxoma. In systole a loud midsystolic murmur representing outflow obstruction was present. In diastole a prominent vibration was heard and recorded. By echophonocardiography this noise could be ascribed to sudden halting of the retrograde excursion of the mass into the right ventricle—a mechanism analogous to the tumor plop associated with the halting of antegrade movement of a left atrial myxoma in the left ventricle in early diastole.

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Fig 6 Photograph of myxoma exposed by incision of the right ventricular outflow tract

A peculiar diastolic sound resembling that reported by us was described and presented in phonocardiograms of only three cases Sakakibara and associates¹² called this sound which was separated by 130 msec from A₂ and abnormal vibratory phenomenon¹³ and Chandraratna and co workers¹ suggested that the sound was a tumor plop rather than P₂ since it was greatly delayed (140 to 160 msec) after A₂. Chandraratna and colleagues observed that the diastolic sound a low pitched thud was coincident with maximum anterior motion of the tumor and with the closure of the pulmonary valve by echophonocardiography Snyder and associates recorded a similar sound and speculated that it might be the delayed closure of the pulmonary valve (150 msec. from A₂). This explanation was subsequently questioned by Levisman⁹ who noted that the sound in question occurred after the v wave of the accompanying jugular venous pulse tracing. It should be noted that in these three cases the myxoma had prolapsed through the pulmonary valve just as in our case.

Our patient had a sound of short duration in mid-diastole. The onset of this vibration coincided with the most anterior position of the tumor in the right ventricular outflow tract by M mode echocardiography. This relationship of the impact of the tumor on the right ventricular wall and the appearance of the sound was confirmed from frame-by-frame analysis of the tumor movement as determined by angiography. We feel that

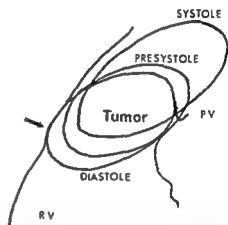


Fig 7 Diagram illustrating the movement of the tumor traced from angiographic frames. In mid-diastole the tumor comes in contact with the free wall of the right ventricular outflow tract (arrow). With atrial and ventricular contraction the tumor is propelled forward through the pulmonary valve (PV). The configuration of the right ventricle (RV) and PV is taken from an angiographic frame in mid-diastole at the moment of impact of the tumor on the right ventricular wall.

this explanation of the genesis of the sound is more reasonable than ascribing it to a much delayed P₂. The sound occurred 150 msec from A₂ which is beyond even the longest separation of A-P in the patients with pulmonary stenosis studied by Leatham and Weitzman.⁹

In view of these considerations the diastolic sound in the reports of Sakakibara and associates and Snyder and colleagues probably also repre-

Torsades de pointes as a manifestation of mexiletine toxicity

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Mexiletine ■ new antiarrhythmic agent, has recently been released for clinical use. Structurally related to lidocaine it belongs to the class of local anesthetic antiarrhythmic agents.^{1,2} Unlike lidocaine however mexiletine is active following oral administration and has a plasma half life varying between 8 and 20 hours.² We report a case of mexiletine toxicity associated with an atypical ventricular tachycardia.

Case report

A 59 year old man was sent to our Cardiological Department University of Ferrara on December 28 1979 with a diagnosis of coronary heart disease (CHD) ventricular arrhythmias and gastrointestinal intolerance to quinidine. A ventriculography in May 1978 had revealed a septal hypokinesia mild cardiomegaly and a left ventricular end diastolic pressure of 23 mm Hg. The left ventricle was abnormal (bulged) by palpation and a 2/6 holosystolic high pitched murmur was heard on the mitral area and at the apex. The electrocardiogram (ECG) revealed a normal sinus rhythm at a heart rate (HR) of 70 beats/minute rare unifocal ventricular premature complexes (VPCs) and non-specific ST-T changes. The PR interval was 0.17 sec the QRS duration 0.09 sec and the QT interval was 0.46 sec. Sitting blood pressure (BP) was 120/80 mm Hg and the patient's weight was 78.5 kilograms. A 24 hour dynamic ECG revealed multifocal VPCs (1 230 in 24 hr) couplets and runs and three sustained runs of ventricular tachycardia (Fig 1). Lidocaine was given intravenously at a 1 mg/kg loading dose followed by 2.5 mg/minute and it reduced the number of VPCs by over 85%. Neither couplets nor runs were observed during the 6 hour therapy and observation period. It was then decided to treat this patient with

mexiletine 100 mg every 6 hr. Since the patient did not present with angina pectoris with the possible exception of perhaps one slight episode during effort every 10 days we decided to treat angina only by sublingual nitroglycerin whenever necessary. No other therapy was prescribed. The patient was requested to come every 10 days for regular checkups. Seven days later the patient came complaining of dizziness occasional palpitations and increasing dyspnoea. A 8-hour dynamic ECG revealed a very good control of the previous VPCs however a new and severe form of ventricular arrhythmia namely a variant of ventricular tachycardia (Fig 2) was detected. At this time the plasma electrolytes were normal potassium 4.4 mEq/L sodium 141 mEq/L calcium 4.9 mEq/L and magnesium 1.6 mEq/L. The physical exam was stopped and two 24 hour dynamic ECGs were obtained. The ventricular tachycardia did not recur but the VPCs increased progressively and 18 hours after stopping mexiletine they reached the number and the type that were previous. The patient was then treated with doxypyramide 100 mg every 8 hr and atenolol 50 mg/day. Three 24 hour dynamic ECGs were obtained at 8- to 15-day intervals. With this therapy the number of VPCs decreased to 65% to 76% and the couplets or runs were no longer observed. Until the time of writing (February 14 1980) the patient felt relatively well and does not complain of palpitations or other symptoms or related symptoms. Ventricular tachycardia has not been observed.

Discussion

This patient's arrhythmia seen during mexiletine treatment represents a variant of ventricular tachycardia and we believe that it fulfills the criteria for the torsades de pointes. We could not document the origin of this torsade de pointes by means of electrophysiological studies. However we believe that it was of ventricular origin. Indeed no P waves were evident. The atrial rhythm resembles some of the patient's previous VPCs. The patient had also had previous episodes of ventricular tachycardia though not

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Note references 4 and 11 deal with the same case

ciated with a variety of cardiac diseases. Its oral effectiveness, its relatively long duration of action, and the relatively low incidence of serious side effects indicate that this drug has its place among the antiarrhythmic agents. However, though rarely mexiletine similar to the other antiarrhythmic drugs of the local anesthetic type may cause the feared torsades de pointes. Until now this side effect had not been observed with lidocaine, and it was therefore surprising that mexiletine electrophysiologically and chemically similar to lidocaine could indeed induce this arrhythmia.

Summary

An episode of torsades de pointes, an unusual ventricular tachyarrhythmia, developed in a 59-year-old coronary patient who was treated with 100 mg four times a day mexiletine orally. The PR, QRS, and QT intervals were normal. The ventricular arrhythmias resembled in part the patient's previous ventricular premature complexes but there were some relevant morphological differences. The plasma electrolytes were within normal limits. Mexiletine, which is chemically and electrophysiologically similar to lidocaine, probably caused this arrhythmia. Although mexiletine is a useful antiarrhythmic drug, it

should be added to the list of drugs associated with atypical ventricular tachycardia.

The authors wish to express their gratitude to M. C. Fin for her secretarial assistance.

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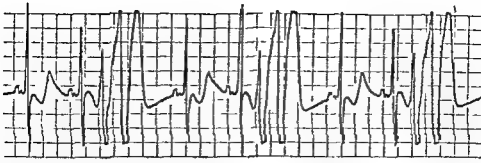


Fig 1A Representative strip of the 24 hour dynamic ECG (bipolar chest lead) prior to mexiletine administration. This strip shows an example of ventricular couplets.

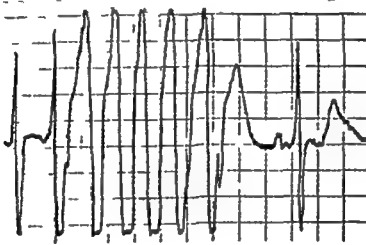


Fig 1B Representative rhythm strip a in Fig 1A. This strip illustrates an example of runs of ventricular tachycardia.



Fig 2 A representative strip of the 8-hour ECG (bipolar chest lead) showing ventricular tachycardia during mexiletine administration.

logically different. The PR and QRS intervals immediately before and after this episode of torsades de pointes were within normal limits and the QT did not appear to be pathologically increased. Since the plasma electrolytes were within normal limits they cannot be held responsible for this arrhythmia. We believe that this torsade de pointes was induced by mexiletine. Quinidine, disopyramide, and also other antiarrhythmics of the local anesthetic type have been found to cause this arrhythmia. However, quinidine generally induces this arrhythmia in conjunction with a QT prolongation. Diso-

pyramide may also prolong the QT interval.⁴ The rare broadening of the QRS complex induced by mexiletine² was not observed in this patient. Although we did not obtain plasma levels for mexiletine there were no signs of toxicity. Furthermore, the patient did not present any signs of renal or hepatic failure. It is therefore unlikely that this side effect was secondary to an excessively high dose of mexiletine.

Conclusions

Mexiletine is a useful antiarrhythmic agent effective against ventricular arrhythmias asso-

ciated with a variety of cardiac diseases. Its oral effectiveness, its relatively long duration of action, and the relatively low incidence of serious side effects indicate that this drug has its place among the antiarrhythmic agents. However, though rarely mexiletine similar to the other antiarrhythmic drugs of the local anesthetic type may cause the feared torsades de pointes. Until now, this side effect had not been observed with lidocaine, and it was therefore surprising that mexiletine electrophysiologically and chemically similar to lidocaine could indeed induce this arrhythmia.

Summary

An episode of torsades de pointes, an unusual ventricular tachyarrhythmia, developed in a 59-year-old coronary patient who was treated with 100 mg four times a day mexiletine orally. The PR, QRS, and QT intervals were normal. The ventricular arrhythmias resembled in part the patient's previous ventricular premature complexes but there were some relevant morphological differences. The plasma electrolytes were within normal limits. Mexiletine, which is chemically and electrophysiologically similar to lidocaine, probably caused this arrhythmia. Although mexiletine is a useful antiarrhythmic drug, it

should be added to the list of drugs associated with atypical ventricular tachycardia.

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Cardioversion and defibrillation

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Historical background

The use of electrical energy for reverting diverse cardiac tachyarrhythmias has in the last 70 years become standard practice because of its safety and reliability. Contemporary clinical cardiology and cardiac surgery have been significantly affected by the ready availability of a simple method for terminating atrial and ventricular arrhythmias. But interest in electricity for medical use is hardly contemporary. Preoccupation with galvanic current both for amusement and for resuscitation can be documented in the eighteenth century.¹ Possibly the earliest case of successful resuscitation was that of a three year old child who was shocked through the chest by a discharge from a Leyden jar by a Mr Squires of London.¹

The earliest recorded experimental approach to the use of electrical shock for resuscitation was that of Abildgaard² in 1770. He shocked hens delivering a sufficient charge to render them lifeless. Subsequent shocks revived the birds and he noted that shocks to parts other than the chest were ineffective. Abildgaard was unaware of ventricular fibrillation (VF) as this arrhythmia was described only in 1849 by Ludwig and Hoffa.³ Based on extensive physiological studies of the heart McWilliam suggested in 1889 that VF was the mechanism of sudden death a conclusion which is sanctioned by contemporary observa-

tions. In 1899 Prevost and Battelli⁴ while investigating the effects of electricity on animals noted that weak currents induced and strong AC or DC currents terminated VF. A reliable method to terminate VF had to await further developments.

With the introduction of the dynamo and the development of commercially available electric power a new industrial hazard emerged. The first electrocution in the USA occurred in 1879 and this number grew rapidly. It soon became apparent that such deaths were due to VF. Kouwenhoven and his colleagues^{5,6} examined both AC and DC circuits for defibrillation and concluded that AC gave superior results. They also studied the effects of chest massage which had been commented on previously by Prevost and Battelli in their defibrillation studies. Ferris and co workers⁷ in 1936 succeeded in closed chest defibrillation in sheep using AC. The culmination of these studies came in 1947 when Beck and colleagues⁸ defibrillated the exposed human heart at surgery with complete recovery of the patient. Closed chest defibrillation in man was first accomplished again using an AC device in 1956 by Zoll and co workers.⁹

Up until the early 1960s AC was thought to be the definitive measure for defibrillation. The earlier work of Gurvich and Yuniev¹⁰ in the Soviet Union and of McKay and Leeds¹¹ in the United States established a basis for the exploration of DC or capacitor discharge. Subsequent investigations by Peleska^{12,13} outlined the physiologic and pathologic consequences of electrical discharge as well as the circuit characteristics for safe defibrillation. Contemporaneous studies by Lown and co workers^{14,15} demonstrated that DC

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especially important to record since immediately following reversion the P waves may be diminutive in the limb leads and the rhythm may be irregular. The interpretation would then be of continued atrial fibrillation if this is the rhythm being treated and the patient is thereby subjected to unnecessary discharges at higher energies.

C Anticoagulation Anticoagulation prior to cardioversion is unnecessary in the patient with the acute onset of atrial fibrillation or if its duration has been less than a week. However many patients who are aware that they have experienced a change in rhythm underestimate the time onset of the fibrillation. Thus in view of the potential for embolic events within this group of patients we routinely anticoagulate patients for a period of three weeks prior to cardioversion. Following cardioversion anticoagulation is maintained for one month. Other atrial arrhythmias do not require anticoagulant drugs.

Termination of specific arrhythmias

1 Atrial fibrillation Prior to the introduction of cardioversion restoration of sinus rhythm was time consuming and hazardous requiring the use of increasing doses of quinidine on successive days. This was carried out until the patient became either very ill or until sinus rhythm was restored. The procedure frequently required a week or more. The initial experience by Lown and co-workers¹ from this laboratory detailed results with cardioversion among 50 patients with 65 episodes of atrial fibrillation. In this group of patients the arrhythmia was successfully terminated in 58 of 65 or 89% of episodes. The results were particularly striking in view of the fact that many of the patients had been in chronic fibrillation over many years that these patients were largely resistant to quinidine reversion and that in a number cardioversion was carried out immediately after mitral valvular operation. Energy requirements for reversion are a function of the duration of the rhythm disorder. Thus patients with atrial fibrillation in excess of six months required a mean energy of 150 wsec while those with AF of less than three months required 100 wsec. The size of fibrillation or P waves in Lead V₁ provides an important clue as to the energy requirement and whether indeed cardioversion will succeed. The energy for reversion is inversely related to the size of the P wave. Thus when

three groups of 50 patients each were segregated as to P wave amplitude those having less than 1 mm amplitude required 140 wsec, in those with dimensions of 1.0 to 2.0 mm 118 wsec was effective while in those exceeding 2.0 mm 97 wsec was required. It is our practice to utilize energies to 400 wsec if necessary. However 95% of patients are usually reverted with 200 wsec or less.

When patients are electrically reverted from atrial fibrillation several outcomes are observed. A fairly common sequence involves long periods of sinus node astyole with junctional escape followed rapidly by sustained sinus bradycardia with a gradually accelerating rate. This has been designated as the 'somniaient sinus syndrome' and reflects recovery of the sinus node from prolonged overdrive suppression by chaotic atrial depolarizations. A less common sequence involves an ever changing sinus rate with differing P wave morphologies. Bradycardia alternating with variable atrial rhythm and multiple atrial premature beats as well as paroxysms of tachycardia are additional hallmarks of this syndrome which Lown designated the 'wicket symptom syndrome'. Generally such abnormalities in generation and conduction of the sinus impulse are observed following cardioversion of patients with atrial fibrillation of several years duration. It frequently augurs the prompt recurrence of atrial fibrillation. Among patients with recent onset of atrial fibrillation neither of the above sequences occurs. A 'strong' sinus rhythm with an unchanging P wave follows within 10 to 30 seconds after the electrical shock. The rate is sustained between 60 to 90 per minute without arrhythmia or interrupted by occasional atrial ectopic beats.

Maintenance of sinus rhythm is facilitated by the use of antiarrhythmic drugs specifically quinidine. We initiate this agent 24 to 48 hours prior to cardioversion in divided doses totalling 1.2 grams daily. Use of quinidine reduces the energy for cardioversion effects a 10% to 15% pharmacologic reversion to sinus rhythm and stabilizes the atrium thereby decreasing the likelihood of post cardioversion recurrence of arrhythmia. The prolongation of the QT interval by quinidine is generally without hazard except in a small number of patients who have mitral valvular regurgitation and a high frequency of ventricular premature beats. These patients are at a higher risk of

selected for triggering the electric discharge. The physiologic basis for cardioversion is that electrical discharge depolarizes part of the reentrant pathway that is non refractory. Once an arrhythmia is initiated it may be self sustaining. Continuation of the arrhythmia may be due to the existence of a reentering wavefront of excitation traversing a fixed or a variable pathway. The advancing wavefront of depolarization is separated from its tail by fully recovered tissue the so-called excitable gap. Depolarization of the excitable tissue in the reentry circuit will eventually close the gap preventing sustenance of the arrhythmia. That such depolarization of the excitable gap is indeed the basis for the effectiveness of cardioversion is supported by the observation that this technique is equally effective irrespective of where in the cycle the discharge is delivered. The above explanation accords with current electrophysiologic understanding. It does not explain however why arrhythmias such as fibrillation or atrial or ventricular require larger energies than those necessary for atrial flutter or ventricular tachycardia.

Method of cardioversion

The procedure should be fully explained to the patient to allay anxiety as the amount of energy required is related to the level of agitation and unease. Cardioversion should be performed following an overnight fast or omitting the previous meal in more urgent cases. Intubation is not necessary. If the patient is on a digitalis drug this medication need not be withheld. Serum levels of digoxin and electrolytes should be obtained on the day prior to the procedure. Prothrombin time is obtained if the patient has been anticoagulated for atrial fibrillation. Cardioversion is preferably carried out early in the day in a room equipped for cardiopulmonary resuscitation. There should be a minimum of personnel and activity. The patient should be warm, comfortable and unencumbered by tight fitting clothes. An intravenous infusion is started for drug administration. Blood pressure is monitored prior to and during administration of the anesthetic. Once the procedure is completed the patient is electrocardiographically monitored for one hour before being released.

A. Anesthesia. Initial sedation is provided by administering 100 mg of phenobarbital intramuscularly an hour before the procedure. The seda-

tion thus provided reduces the amount of diazepam (Valium) to be given subsequently. At the time of cardioversion an initial intravenous dose of 5 mg of diazepam is administered followed by 25 mg increments every two to three minutes. Both blood pressure and respiratory rate are monitored prior to each dose. The average amount of diazepam required to achieve adequate sedation with amnesia in over 500 cardioversions was 15 mg although the range is quite variable and up to 50 mg may be administered without ill effects.

B. Cardioversion technique. The main danger in transthoracic electric discharge is the provocation of VF. The current generation of cardioverters incorporates an automatic mode which displays and inscribes the precise location of the capacitor discharge on the R wave. The lead which best displays the highest R wave amplitude should be selected for discharge synchronization. The risk of provoking ventricular fibrillation in a nonsynchronized discharge is less than 5%. Improper synchronization may result when the electrocardiographic signal contains artefactual spikes when there are extremely prominent T waves and in bundle branch block when the R wave is taller than the R wave.

Both anteroposterior and anterolateral electrode positions have been employed in cardioversion and defibrillation. The anteroposterior position reduces energy requirements by 50% and thus potential complications are reduced. The anterior electrode is held firmly along the right sternal border at the level of the second and third intercostal spaces while the posterior electrode is placed at the angle of the left scapula. The electrodes must be completely covered with conductive gel particularly along the edges to reduce the likelihood of skin burns.

During elective cardioversion energy titration should be employed with an initial setting at 5 wsec. Low energies may disclose rhythm disturbance in patients with subclinical digitalis toxicity or electrolyte disturbance and may also reduce myocardial damage. The emergence of ventricular arrhythmia in such circumstances requires prompt use of lidocaine. The procedure is then continued utilizing increasing energies of 10, 25, 50, 100, 200, 300 and 400 wsec until reversion occurs. After each successive discharge monitor mg of Lead II or V, will assist in defining the resumption of sinus rhythm. The latter lead is

necessity in these cases. In many of these patients we deliberately attempt to induce this chronic rhythm disorder as the rhythm of choice.

2 Supraventricular tachycardia. The majority of supraventricular tachycardias (SVT) do not require cardioversion as they usually respond to vagal maneuvers. Vassilux and Lown³ found that patients coming to cardioversion for SVT had been hospitalized with this arrhythmia for several days and had failed to revert despite the use of a variety of antiarrhythmic agents. There has been a reluctance to employ cardioversion for the patient with organic heart disease who experiences SVT. In part this is due to the fact that digitalis overdose may be responsible for paroxysmal atrial tachycardia with or without block. Cardioversion of such patients may be hazardous. Indeed, death has been reported following cardioversion in patients with digitalis induced supraventricular mechanisms.^{3,33} Yet the greatest urgency for reversion to normal rhythm may exist in patients with these very arrhythmias. Since these arrhythmias frequently occur in patients with substantial organic heart disease and significant congestive manifestations, the rapid ventricular rate encroaches further upon an already compromised ventricular reserve. If the mechanism is due to digitalis intoxication, cardioversion is contraindicated. If however the likelihood of such intoxication is remote, cardioversion is the measure of choice. Titration of energy permits safe reversion of digitalized patients with SVT.

Occasionally, clinical circumstances do not clearly define the presence of digitalis toxicity. Cardioversion may then be employed as a diagnostic modality. The emergence of ventricular ectopic activity or higher degrees of atrioventricular block without reversion to sinus rhythm at low energies strongly suggest digitalis toxicity. When ventricular arrhythmias are provoked, these are promptly controlled with intravenous lidocaine. If after successive discharges the ectopic mechanism is not abolished but ventricular ectopic beats increase in frequency, multifocal and repetitive pattern, it is likely that overdigitalization is the underlying condition and it is best to desist from further attempts at cardioversion.

3 Atrial flutter. Prior to the advent of cardioversion, atrial flutter was considered the most difficult arrhythmias to manage. Although the mechanism for this arrhythmia has not been definitely

established, clinical and experimental evidence indicates that it is the result of a circus movement as defined by Lewis and associates.³ The arrhythmia is often refractory to the conventional antiarrhythmic agents including quinidine, procainamide, propranolol and disopyramide. Large and often toxic doses of digitalis glycosides may be required in order to obtain ventricular rate control and even then difficulty in producing consistent block at the atrioventricular junction results in episodic ultra rapid rates with troublesome palpitation. It may be life threatening if 1:1 A-V conduction should develop. Cardioversion is now the method of choice for terminating atrial flutter. Numerous reports have documented that this technique is 72% to 100% effective.^{3,33,34} Lown³ found that atrial flutter is successfully terminated in 97% of cases. The effective energy is generally less than 50 wsec with the average requirement of 1/3 wsec in 1 of 200 patients studied with this arrhythmia. Usually only a single discharge is necessary.

When atrial flutter is recurrent notwithstanding the use of antiarrhythmic drugs, when the arrhythmia recurs shortly after successful cardioversion, or if cardioversion is unsuccessful in restoring normal sinus rhythm, it is our practice to attempt to establish atrial fibrillation as the rhythm of choice. This can be accomplished by the use of large doses of digitalis glycosides following which atrial fibrillation may emerge. Another therapeutic option is to utilize a low energy discharge during cardioversion. This technique is more effective and carries less morbidity. Experimental and clinical data have shown that if a stimulus is applied to the vulnerable period of the atrium, atrial fibrillation will occur.³⁵ Since flutter is likely to be a reentrant mechanism, some parts of the atria are always undergoing depolarization while other parts are in a state of refractoriness or incomplete repolarization. Thus, the vulnerability to fibrillation is present throughout the flutter cycle and a low energy discharge given at any time in the cardiac cycle stimulating some incompletely recovered atrial tissue will convert atrial flutter to fibrillation. About 50% of subjects with atrial flutter will receive such low energy discharges will develop atrial fibrillation if the shock is inadequate to restore sinus rhythm. The median shock necessary to induce fibrillation with this method is 15 wsec with a range of 1 to 20 wsec.

experiencing quinidine syncope. It may be wise to substitute another antiarrhythmic agent in these cases. Maintenance of sinus rhythm beyond 12 months is accomplished in less than one half of patients with atrial fibrillation.⁴⁷ This is particularly true for the patient whose atrial fibrillation is associated with altered left ventricular function.

Determination of which patients are suitable for elective cardioversion from atrial fibrillation requires careful assessment of the patient and knowledge of contraindications of the procedure. Cardioversion may not succeed or is relatively contraindicated in the following groups of patients with atrial fibrillation:

(a) *Atrial fibrillation of prolonged duration*
Higher energies are required for reversion of atrial fibrillation of prolonged duration and the success rate is low. We generally limit elective cardioversion to patients who have been in chronic atrial fibrillation for less than one year. In those with arrhythmia of longer duration, sinus rhythm is unlikely to persist in more than half the patients.^{48, 49}

(b) *Mitral valvular disease with markedly enlarged left atrium*
Chronic mitral regurgitation or stenosis alters both the size and mean pressure of the left atrium. This provides conditions for a sustained fractionation of reentrant excitability and is particularly the case in those having a giant left atrium secondary to mitral regurgitation. Prior to the onset of atrial fibrillation a number of these patients will have exhibited first degree atrioventricular block and frequent atrial premature beats, which are associated with relapse of atrial fibrillation. While reversion to sinus rhythm is simple, maintenance of a normal mechanism with current antiarrhythmic drugs is often difficult or even impossible.

(c) *Atrial fibrillation in the setting of left ventricular failure*
The patient experiencing altered left ventricular function may develop acute atrial fibrillation secondary to elevated left-sided filling pressures and subsequent atrial distension. This may be the clinical setting of a patient with an acute myocardial infarction. In this situation the use of digitalis drugs to decrease the ventricular response to atrial fibrillation thus improving ventricular function will usually result in restoration of sinus rhythm. Myocardial infarction is however not a contraindication for electrical reversion. Cardioversion

carried out in the patient with severe pulmonary congestion will probably not restore sinus rhythm especially when atrial fibrillation was not the initiating factor. Occasionally a patient with a far advanced cardiomyopathy who is anticoagulated will benefit from the augmentation of cardiac output derived from even a brief period of sinus rhythm. Hence the management of this type of patient might include periodic cardioversion.

(d) *Lone atrial fibrillation*
Atrial fibrillation is not uncommon in the absence of demonstrable heart disease. The left atrial and left ventricular chambers are usually normal in size and fibrillatory waves are diminutive in Lead V₁. Maintenance of sinus rhythm is difficult despite the use of antiarrhythmic agents and cardioversion is of limited application. However there exist no prior methods for ascertaining the patient who will sustain sinus rhythm for either long periods or even permanently. It is therefore worthwhile to subject such patients to at least one cardioversion.

(e) *Atrial fibrillation with a slow ventricular response*
The majority of patients with acute atrial fibrillation exhibit a ventricular response in excess of 130 beats/minute. Frequently one encounters an elderly patient not receiving digitalis or beta adrenergic blocking agents whose ventricular response is 70 beats/minute or less. The absence of tachycardia most probably reflects the coexistence of atrioventricular conduction disturbance. Reversion to sinus rhythm may be associated with extreme bradycardia requiring the use of a permanent pacemaker. Atrial fibrillation is far preferable in these cases.

(f) *Adverse reaction to antiarrhythmic agents*
Maintenance of sinus rhythm following cardioversion requires the use of chronic antiarrhythmic therapy. Thus patients who are unable to tolerate antiarrhythmic drugs such as quinidine or disopyramide or who experience a recurrence of arrhythmia on these drugs may not be candidates for cardioversion.

(g) *Recurrent atrial tachyarrhythmias*
Patients with chaotic arrhythmias (Parkinson-Papp syndrome) or those with oft recurring atrial tachyarrhythmias flourish once atrial fibrillation becomes established. They no longer are disabled by the frequent paroxysms with the onset of atrial fibrillation. Thus atrial fibrillation is the preferred rhythm and becomes a therapeutic

chest massage and correction of acid base balance delivery of two or three 400 wsec shocks in rapid sequence as a last resort may be successful

Reversion during pregnancy Pregnancy may be the setting for recurrent atrial arrhythmias which may be resistant to pharmacologic therapy and cardioversion.⁸ However both elective and emergency reversion have been performed with safety during all three stages of pregnancy.¹²⁻¹⁷ Schroeder and Harrison¹⁸ reported seven episodes of cardioversion for PAT in one patient during various stages of pregnancy. In all attempts 100 wsec terminated the abnormal rhythm. Grand and Bernard¹⁷ used 300 wsec to revert atrial fibrillation successfully without disruption of fetal heart rhythm. However suspected fetal distress necessitated cesarean section for delivery. In other reports¹¹⁻¹³ cardioversion did not induce premature labor. Defibrillation during pregnancy presents no real therapeutic dilemma as death of the mother and the fetus will almost certainly supervene otherwise. Curry and Quintana⁹ reported the successful termination of VF during acute myocardial infarction with a single 300 wsec shock. The fetal ECG was unaffected by the discharge but the mother was subsequently found dead presumably as a result of recurrent VF.

Fetal rhythm should be monitored during cardioversion. Induction of VF by the electrical discharge during the fetal ventricular vulnerable period is remote and the energy reaching the fetal heart is minuscule. Furthermore it is known that the hearts of small mammals can be fibrillated only with great difficulty and the disordered rhythm is often self terminating. This is presumably because a critical myocardial mass is necessary to sustain VF.

Complications

Morphologic and functional damage A large number of studies demonstrate that electrical discharge causes both morphologic and functional derangements. Grossly recognizable as well as microscopic damage may occur.^{2,3,4,5,6,7} Lown and colleagues¹⁹ demonstrated progressive changes consistent with the release of tissue potassium as successive high energy shocks were delivered. Electrically induced tissue damage is considerably less with DC as compared to AC shocks.²¹⁻²³ Dahl and co workers²⁴ quanti-

fied myocardial damage by precordial mapping and by gross and microscopic pathologic studies in dogs. Myocardial damage was greatest when small electrodes were used and when shocks were closely spaced. They recommended that during elective cardioversion shocks be spaced at intervals of more than 3 minutes to spare the heart from damage. Davis and co workers²⁵ found that if energy levels less than twice the threshold strength necessary for defibrillation were delivered minimal myocardial damage occurred in dogs. Progressively more severe necrosis occurred with increase in delivered energy. In a similar study Van Vleet and colleagues²⁶ concluded that a relatively broad safety margin existed between the threshold energy required for defibrillation and the energy levels which produced significant cardiac damage and death in healthy dogs. Warner and co workers²⁷ found areas of permanent cardiac damage as evidenced by scarring and calcification following repeated shocks. Lesions were characteristically subepicardial.

Following electrical shock there is release of myocardial creatine phosphokinase (MB CPK) as well as other enzymes. In man myocardial damage has been examined during elective cardioversion.²⁸ None of 27 patients who received less than 425 wsec either in single or cumulative shocks demonstrated a rise in MB CPK. In two of three patients who received a cumulative delivered energy dose of more than 425 wsec MB CPK was elevated. Myocardial scintigraphic studies likewise confirm that the extent of damage in dogs subjected to shocks was proportional to the quantity of energy delivered to the heart.²⁹ It is clear from the numerous studies cited that myocardial damage certainly occurs especially with repeated high energy shocks. The use of high energies with inadequate skin preparation also leads to painful skin burns. Imperfect technique with proper electrode position and adequate conductive paste should therefore be used at all times.

In addition to morphologic damage functional derangements result from electric shocks. Fink³⁰ noted intracardiac temperatures as high as 47° C after shocks to the exposed heart. Depression in left ventricular function and contractility may result.³¹⁻³³ Koning and colleagues³⁴ showed that isolated perfused hearts decrease in dp/dt as an increase in diastolic stiffness and left ventricular diastolic pressure following electric shocks.

4 Ventricular tachycardia Ventricular tachycardia (VT) may be due to an ectopic focus or to a reentrant mechanism. Enhanced automaticity is the basis for ventricular tachycardia resulting from digitalis intoxication or during the initial period following acute myocardial infarction. However the most frequent mechanism is reentry. This suggests that cardioversion may be useful for terminating a majority of these episodes. Since the first reported case of ventricular tachycardia reverted with AC shock, electrical discharge has become the standard and routinely employed therapeutic measure. Cardioversion should be used expeditiously in the critically ill patient with ventricular tachycardia associated with hypotension, pulmonary edema or an acute myocardial infarction when intravenous lidocaine has failed. The reported success rate varies from 95% to 100%.^{3, 5, 20} The energy requirements are almost always less than 100 wsec. As little as 1 wsec will convert some cases of ventricular tachycardia, and in 80% of cases 10 wsec or less has proved adequate.⁴

When ventricular tachycardia is rapid and the QRS complex is wide and bizarre in configuration, a broad prominent T wave may not be distinguished from the QRS complex. The disorder has been termed ventricular flutter of VT of the vulnerable period (VT). Cardioversion affords a 50% chance that the discharge will occur at the apex of the T wave instead of during inscription of the R wave. In fact, instead of avoiding the vulnerable period, the shock is synchronized to fall precisely during its midst. When confronting such a problem it is advisable to switch to the defibrillator mode and deliver a nonsynchronized shock of 100 wsec. This practice diminishes the likelihood of provoking ventricular fibrillation.

5 Ventricular fibrillation The vast majority of cardiac arrests are due to VF.²¹ Defibrillation constitutes definitive treatment for this condition and success is assured only if prompt defibrillation is accomplished. Although the ideal electrode positions are not known in man, it is reasonable to assume that they will approximate those for elective cardioversion of atrial and ventricular arrhythmias.

Initial defibrillation in adults should be conducted with a setting between 300 to 400 wsec. Lower energy settings with rapid sequential discharge as practiced by some workers² should

preferably be employed only if the resuscitation team is highly experienced. Valuable time may otherwise be lost due to inefficient or improper application of the procedure. Some newer defibrillators may have energy settings in excess of 400 wsec. Such devices should be used with care as the possibility of serious cardiac damage and complications is increased. The initial setting should never exceed 400 wsec. At present there is no evidence that energies in excess of 400 wsec are ever needed in man for defibrillation. If higher energies are used, prolonged periods of asystole or complete heart block may ensue, resulting in resumption of VF. Repeated shocks with high energy result in resumption of VF due to progressive myocardial deterioration, ultimately rendering termination of VF impossible.

Clearly the above recommendations are excessive for pediatric subjects. Gutgesell and colleagues, in studying 27 children weighing between 2.1 to 50 kilograms, terminated 63 of 71 episodes of VF with shocks up to 300 wsec. A setting of 2 wsec/kg \pm 10 wsec was used for most of the episodes and 91% of shocks in this range were successful in terminating VF. Five of the eight failures in this series of patients occurred with the recommended energy level, two occurred at lower settings and one at a higher setting. The authors caution that rebrillation is not an indication to increase the energy dose. At the present time there are inadequate data to make definitive recommendations for pediatric defibrillation. However, experience to date indicates that repeated high energy shocks are inappropriate, especially for small children. Defibrillation of the heart during open chest surgery is another setting where low energy shocks are used. In most situations, shocks of 5 to 10 wsec are adequate.

Ventricular fibrillation of prolonged duration may be resistant to electric shock regardless of the amount of energy used. In this situation repeated high energy shocks produce momentary asystole with resumption of fine-grain VF. Such a situation requires correction of acid base imbalance and hypoxia before further attempts are made. Administration of a beta adrenergic agent such as epinephrine or isoproterenol may convert a fine-grain pattern to coarse grain VF. The latter variety of VF is more susceptible to electrical termination. If repeated single shocks fail to terminate VF despite adequate ventilation

following cardioversion had mitral or aortic valvular disease or left ventricular dysfunction. Increase in cardiac output with return of atrial systole following cardioversion^{100, 106} and concomitant depression in left ventricular function by electric shocks may be contributing factors to the development of heart failure. Occasionally return of left atrial systole is delayed after cardioversion so that the disparity in outputs of the right and left sides of the heart may be expected.^{91, 10, 111} This may lead to an increased volume load on the left ventricle resulting in pulmonary edema.

g Embolism Approximately 30% of patients with atrial fibrillation may experience spontaneous serious embolic episodes during their lifetime.¹¹ The risk of embolism is increased immediately following both pharmacologic or electrical reversion to sinus rhythm. In 400 patients reverted with quinidine Goldman¹¹³ encountered an incidence of 15%. Pulmonary as well as systemic embolization may also follow cardioversion.^{113, 114, 115, 116, 117, 118, 119} The majority of patients experiencing this complication were not receiving anticoagulants prior to cardioversion. The incidence of embolism in 450 episodes of atrial fibrillation treated with cardioversion was approximately the same as following reversion with quinidine at 12%.¹¹³ None of 100 patients on anticoagulants experienced embolism as a complication. Postponed resumption of atrial systole may account for the delayed embolism occurring several days to a week after cardioversion. Ikram, Nixon and Arcan¹²⁰ demonstrated delayed return of left atrial activity for 3 to 6 days and in one case no atrial activity was detected for 6 weeks following cardioversion. Absence of mechanical activity in left right or both atria has been commented on by other workers as well.^{14, 11, 111} Thus anticoagulation should be performed not only 2 weeks before but also for at least 1 week following cardioversion.

f Miscellaneous complications Resnekov and McDonald¹²¹ noted hypotension following cardioversion in 37 of 220 patients. Decrease in blood pressure is usually transient but may last several hours and generally requires no treatment. Transient cardiac enzyme elevation and ST segment and T wave changes not necessarily related to significant myocardial damage may also occur.^{122, 123, 124} There is little information on the effects of electric shock in producing failure of

implanted artificial pacemakers.^{125, 126} However, this complication has been rarely encountered and therefore should not impede cardioversion.

Damage to adjoining as well as remote structures has been reported as a consequence of the electrical discharge. Pericarditis,¹²⁷ ocular damage,¹²⁸ transient left recurrent laryngeal nerve paralysis¹²⁹ and vertebral fracture¹³⁰ have been described. Some of these complications are due to the physical trauma resulting from body movement following high electrical energy discharges.

Controversies in defibrillation

a Energy dose for defibrillation Tacker, Geddes and their co-workers^{131, 132} have indicated that conventional devices storing 300 to 400 wsec are inadequate to defibrillate adults weighing over 70 kilograms. Geddes and associates found that in animals the threshold energy for defibrillation increased with body weight. Tacker and colleagues¹³³ reported on a series of 111 patients in whom defibrillation success ostensibly declined with increase in body weight. They derived a dose response curve based on 13 subjects and concluded that a third of patients weighing over 70 kilograms could not be defibrillated. They recommended a dose of 35 to 6 wsec/kg for successful defibrillation. This opinion is not persuasive and the evidence concerning it has been presented elsewhere.¹³⁴ The data of Tacker and associates¹³³ and of Collins and colleagues,¹³⁵ the latter being merely an expansion of the former study, were collected retrospectively and provided no information on electrode position, duration of fibrillation underlying heart disease or estimates of delivered energy. Furthermore, statistical analysis of the data they provide does not support their claim that heavier patients were more difficult to defibrillate. In contrast to these data, Kerber and Sarnat¹³⁶ showed in their detailed retrospective study that defibrillation success bore no relation to body weight. On the contrary, their data suggested that use of higher energies was associated with decreased survival.

Numerous studies show that heavy patients can indeed be defibrillated using conventional devices storing 400 wsec. Several case reports^{137, 138, 139} attest to the successful reversion of VF in heavy patients. Prospective studies on VF by Pantridge and co-workers¹⁴⁰ and by Crumpton and associates¹⁴¹ and using devices storing

Release of potassium CPK acetylcholine and catecholamines following shocks may also occur.¹ Regan and associates² found high levels of potassium in coronary sinus blood following transthoracic shocks to the digitalized heart. The quantity of potassium released was proportional to the electrical energy delivered to the heart and they concluded that potassium release by electric shock was enhanced in the presence of digitalis glycosides.

Cardiac arrhythmias. Peleska³ showed that the energy content of the shock was related to both the extent of morphologic damage as well as the severity of ventricular arrhythmia. Lown and co-workers^{4,5} noted in dogs that 3% exhibited ventricular tachycardia after a single 100 wsec shock while 25% showed this arrhythmia after 200 wsec and 65% after 400 wsec. Subsequent studies confirmed that ventricular arrhythmias could be evoked following defibrillation or cardio-

version.^{3,4,6} In man a variety of arrhythmias have been described ranging from ventricular premature beats, bigeminy, salvos of multiple focal beats, ventricular tachycardia and fibrillation. These arrhythmias need not be a consequence of myocardial damage alone. When VF occurs during cardioversion it is usually due to improper synchronization. However, a number of reports document the emergence of VF sometimes leading to death several minutes or even hours after the shock.⁷ These patients had been receiving quinidine, digitalis glycosides or both at the time of onset of VF and these drugs have been implicated in provoking this arrhythmia.^{8,9}

Digitalis intoxication in particular greatly sensitizes the heart to electrical discharge.^{2,10,11,12,13,14} In dogs an eight thousandfold increase in sensitivity to electric shock occurred following administration of a toxic dose of ouabain as judged by the emergence of repetitive ventricular activity.¹⁰ It required 60% to 80% of the toxic dose of ouabain to demonstrate such sensitization. In man Kleiger and Lown⁷ found that 18 of 100 digitalized patients undergoing cardioversion showed frequent ventricular premature beats, bigeminy or ventricular tachycardia. In comparing these 18 patients with the remaining 82 the pre cardioversion electrocardiograms of the former group showed more frequently arrhythmias suggestive of digitalis toxicity. These arrhythmias included ventricular pre-

ature beats, junctional rhythm with or without atrioventricular dissociation and first degree heart block. Two patients also had episodes of atrial tachycardia with block. Patients in atrial fibrillation with ventricular rates of less than 70 per minute and episodic regularization of rhythm had an almost 50% risk of developing ventricular arrhythmias following cardioversion. The grade of arrhythmia increased as a function of the discharged energy.

The patients who developed VF and died as reported by Rabbino and colleagues¹⁵ and by Ross¹⁶ had also received high doses of electrical energy in the presence of digitalis toxicity. This experience underscores the extremely hazardous nature of high discharge energies in overdigitalized patients. The mechanism whereby digitalis sensitizes the myocardium to electrical shock is not clear. Lown, Black and Moore¹⁰ hypothesized that electrical shock alters cation transport across cell membranes promoting efflux of cellular potassium. Such losses are enhanced in the excessively digitalized heart thus promoting the emergence of life threatening ventricular arrhythmia. The studies by Regan and colleagues on dogs digitalized with acetyl strophanthidin and shocked electrically provide experimental support for this hypothesis. Although quinidine facilitates reversion in atrial fibrillation pretreatment with quinidine prior to cardioversion clinically has not been shown definitively to be protective against the development of subsequent ventricular arrhythmias.¹⁷

Electrical discharge can induce relatively more benign arrhythmias such as atrial ectopic beats and impaired atrioventricular conduction. Complete heart block following cardioversion or defibrillation may also occur and its duration is a function of the amount of energy delivered. Use of energies of the order of 300 to 400 wsec however may result in prolonged periods of heart block or asystole which favor the reemergence of ventricular arrhythmias including fibrillation.

Pulmonary edema. Resnekov and McDonald¹⁸ reported on the occurrence of pulmonary edema in four patients within 24 hours of cardioversion. Subsequent studies have confirmed this finding.^{19,20,21,22} Among 750 patients we have seen three patients with pulmonary edema and these had pulmonary embolism. It is uncertain if additional mechanisms are involved. The majority of patients reported with pulmonary edema

Subsequently a single catheter system with two sets of electrodes on the same catheter has been developed. The sensing unit consists of either a pressure transducer or a contraction sensor element as an integral part of the catheter. The capacitor charges itself if there is absence of detectable pressure or right ventricular contraction and discharge occurs after a preset interval if either of these two conditions persists. Preliminary studies show that the method is effective in defibrillating both animal and human hearts using energies from 4 to 35 wsec.

Intriguing though the concept is, Lown and Axelrod²¹ have questioned the merit of implanted defibrillators. They point out that malfunction may result if the sensing element should become encased in fibrotic tissue or if the catheter migrates into the pericardial sac. Unnecessary and possibly lethal shocks may then be delivered. Even if these problems are overcome, the question of periodic evaluation for adequacy of performance remains. Unlike pacemakers which can easily be functionally assessed, implanted defibrillators cannot be so evaluated. Verification of adequacy would include not only ascertaining activation of the device exclusively by VF but delivery of a charge sufficient to defibrillate the heart. For the present, more conventional approaches to the problem of sudden death from VF are preferable.

Summary

The use of electrical energy for the immediate treatment of atrial and ventricular arrhythmias is practical and easily applied. The method though simple is the most effective method for terminating cardiac arrhythmias and is associated with only a low risk if properly employed. In symptomatic patients the utilization of cardioversion reduces patient discomfort and complications which may occur while awaiting pharmacologic reversion of arrhythmia. At present, transthoracic defibrillation is the only practical method for terminating VF. Despite the safety of electrical reversion, proper precautions are necessary to prevent complications. In particular, the discharge of excessive energies especially in the presence of digitalis toxicity promises grave and life-threatening consequences. The use of antiarrhythmic medications is not supplanted by cardioversion and defibrillation. Rather, ongoing

drug therapy is frequently necessary to prevent recurrence of arrhythmia.

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400 wsec or less reverted over 95% of patients with VF. These workers used either single or multiple or low energy shocks and the mean energy required for defibrillation was frequently 50% less than that recommended by Tacker and colleagues.¹¹ When shocks of 200 or 300 wsec failed, 400 wsec almost invariably succeeded. Crampton and his group⁶ found that a mean energy of 194 wsec terminated 45 of 46 episodes of VF in 11 of 12 heavy patients. The patients weighed between 91 and 225 kilograms and the mean energy requirement was 18 wsec/kg. Conventional devices storing 400 wsec thus appear to be adequate for clinical use. Delivery of higher energies while likely to induce injury has yet to be shown to be necessary.^{12,13}

ii Blind defibrillation. Grace and co workers¹⁴ have suggested that when encountering cardiac arrest immediate discharge of 200 to 400 wsec be performed in the absence of electrocardiographic confirmation of VF. They argue that since VF is implicated in the vast majority of patients having an arrest, prompt defibrillation provides the greatest chance for full recovery. Although a controlled study was not performed, they noted an increase in survival rates from 27% to 45% after blind defibrillation was started in their institution.

If cardiac arrest has been presumed to exist by virtue of loss of consciousness and absence of a pulse, the mechanism may be VF, asystole, or electromechanical dissociation. The majority of patients, however, have been found to be in VF. Prompt defibrillation will constitute definitive therapy with a minimum of delay. A possible hazard exists in a very small minority of patients that they may be shocked during the ventricular vulnerable period while in rhythms other than VF. If the mechanism is ventricular tachycardia, use of high energies (300 to 400 wsec) will terminate the disorder rather than provoke VF. This is due to the fact that a high energy discharge uniformly depolarizes the entire myocardium when discharged during the vulnerable period. Blind defibrillation with such energies is thus an acceptable risk. Electromechanical dissociation during a cardiac arrest usually signifies an unfavorable outcome. In such an event, it is unlikely that blind defibrillation will exert a deleterious effect on survival. The uncertainty regarding the underlying rhythm disorder is resolved if the

defibrillator electrodes also function as electrocardiographic monitoring leads providing confirmation of the rhythm immediately before discharge.

c Chest thump. Pennington, Taylor, and Lown¹⁵ recommended thumpversion for malignant ventricular tachycardia. They found that a precordial blow reverted 12 episodes of ventricular tachycardia in five patients, in three of whom myocardial infarction was the basis for the arrhythmia. The electrophysiologic basis for thumpversion is unknown. However, certain observations made during cardioversion suggest an explanation.¹⁶ The prebrillatory arrhythmia designated ventricular tachycardia of the vulnerable period (VT) can be terminated with less than 1 wsec. Energies less than 10 wsec will terminate over 90% of episodes of VT.¹⁷ Since the small amount of energy delivered by a precordial blow is frequently sufficient to depolarize enough myocardium and initiate a propagated response by electromechanical transduction during cardiac arrest due to asystole,¹⁸ it is likely that during VT depolarization by such a blow may be adequate to interrupt a reentrant pathway and thus terminate VT. Undue delay, however, may result in degeneration of VT to VF. The steep rise in energy requirement for termination of VF then renders chest thumping ineffective.

An objection to this method of reversion has been raised, namely that a thump delivered during the ventricular vulnerable period may result in VF. The possibility of this event occurring is less than 5%. In the hospital, the ready availability of a defibrillator should enable electrical termination of VF. If the patient has lost consciousness, cardiopulmonary resuscitation will be initiated in any case so that an immediate chest thump may be beneficial if the underlying arrhythmia is asystole or VT. However, the present recommendation of the American Heart Association is that chest thump be reserved for monitored patients only.

d Implanted defibrillators. In recent years a number of workers have demonstrated that defibrillation through an intracardiac catheter system is feasible.¹⁹ The system consists of an intracavitary right ventricular catheter containing one electrode at its tip and another in the superior vena cava, alternatively a precordial subcutaneous plate may serve as the other electrode.

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Rickettsial vasculitis

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Important rickettsial diseases of man are distributed over all the continents with the exception of Antarctica. In order to approach these diseases their etiologic agents must be defined taxonomically. Definition of the term rickettsia varies from a nearly meaningless inclusiveness of almost any intracellular microorganism to a narrower consideration of only the genus *Rickettsia*. In this discussion the other related genera *Coxiella* (Q fever) and *Rochalimaea* (trench fever) will be excluded. Members of genus *Rickettsia* share the following characteristics: gram negative bacterial ultrastructural morphology, obligate intracellular parasitism, ecologic niche including all or a portion of life spent in an arthropod host and serologic grouping relationships. There are three serologic groups: typhus group, spotted fever group, and scrub typhus group. The concept that rickettsiae are an intermediate form of life between viruses and bacteria is completely outmoded. That they are clearly a specialized group of bacteria is confirmed by method of replication (binary fission), content of both RNA and DNA, ultrastructural morphology, and sensitivity to antimicrobial agents. Although rickettsiae are capable of penetrating and growing within a wide variety of host cells of various species and organ sources in man, they are found only in vascular endothelium and in some diseases, vascular smooth muscle. This anatomic distribution determines the basically similar pathology (vasculitis)

and pathophysiology (increased vascular permeability) of the rickettsial diseases.

Geographic distribution of rickettsial diseases reflects the distribution of infected arthropod hosts and their contact with man. Rickettsial diseases of man, their etiologic agents, vectors, and geographic distribution are presented in Table I.

Although other rickettsiae have been described in various niches in the United States, at this time only *Rickettsia rickettsii* (Rocky Mountain spotted fever), *Rickettsia mooseri* (murine typhus), *Rickettsia prowazekii* (recrudescence typhus), and *Rickettsia akari* (rickettsialpox) have been documented as etiologic agents of disease in man in recent times. Evidence indicates the epidemic typhus has probably been transmitted to man from a natural zoonotic cycle of *Rickettsia prowazekii* in flying squirrels in the southern states, and that *Rickettsia canadensis* possibly causes a disease similar to Rocky Mountain spotted fever. However, in current reports, Rocky Mountain spotted fever (RMSF) accounts for more than 90% of rickettsial diseases with murine typhus a distant second in incidence and the others apparently quite rare.

The incidence of RMSF has risen to a high level with continued significant mortality. In 1950, 199 cases were reported, and by 1968 the total was still only 298 cases. Since that time, a remarkable increase has occurred, peaking at a total of 1,153 cases in 1977. Expressed as a rate, this is a rise from 0.11 cases per 100,000 population in 1959 to 0.50 cases per 100,000 population and 1.66 cases per 100,000 in the South Atlantic states in 1977. Although the mortality rate has fallen from 20% in the preantibiotic era, it has remained in the 5 to 10% range to the present, despite the efficacy of tetracycline and chloramphenicol. RMSF has been reported from 1

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macules which are from less than one to five millimeters in diameter blanch completely and temporarily on pressure and are rarely tender. Subsequently these lesions acquire a deep red to purple hue and increase in size even becoming confluent in some cases. After 2 to 3 days from its onset the rash becomes nonblanchable and petechial. In severe cases during the third week necrosis of dependent peripheral parts including scrotum, prepuce, fingers, toes and external ear may occur.

Study of the pathologic lesions in rickettsial disease has been performed most comprehensively in epidemic louse borne typhus. Wolbach who already had extensive experience in investigating RMSF was sent to Poland with the Typhus Research Commission during World War I. His descriptions based on the study of skin from 36 necropsies and skin biopsies from 28 patients covered the range from the first day of rash to the twenty fourth day of disease.¹⁴ At the onset of rash (day 3 of disease) the only pathologic lesion was swelling of the endothelium of capillaries and small arteries and veins of the papillary and reticular dermis. Rickettsiae were observed in swollen endothelial cells. On day 5 of the disease arterioles and venules demonstrated mural thrombi overlying swollen endothelial cells which frequently contained numerous rickettsiae. Perivascular reaction was minimal. Subsequently contiguous spread of rickettsiae with accumulation of increased quantity of organisms was observed in serial sections, moreover the pathologic lesions involved larger vessels in the deep dermis and subcutaneous tissue and included more prominent perivascular mononuclear inflammation. Dermal hemorrhages were observed around capillaries and vessels of pre capillary size on and after the eighth day of illness. Organization of vascular thrombi was seen as early as the fifteenth day. Areas of gangrene were demonstrated microscopically not to be accompanied by thrombosis of large vessels but to be due to thrombosis of capillaries and small arteries and veins beginning in the dermis and extending centripetally.

Comparison of the lesions of typhus and RMSF is most remarkable for their similarity. However differences which comprise more extensive destruction of the vascular wall including the media and less pronounced perivascular inflammation in RMSF reflect in action of vascular smooth

muscle by *Rickettsia rickettsii* and not *Rickettsia prowazekii* and the generally shorter course of fatal cases of RMSF.

Rarely in any disease are the pathologic lesions correlated so closely with the clinical picture. A careful study of the patient's clinical record will reveal a very close correlation between the microscopic findings and the physiologic disturbances although the latter may be out of all proportion to the visible anatomic lesions.¹⁵ These comments by Harrell in his review of RMSF in 1949 certainly apply to the physiologic disturbances in the peripheral circulation in the more severe rickettsial infections such as epidemic typhus, scrub typhus and RMSF. In 1944 Harrell referring to RMSF¹⁶ and Woodward referring to epidemic typhus¹⁷ postulated in separate publications that hypotension and circulatory collapse seen at the height of these rickettsial infections resulted not from cardiac weakness but from peripheral circulatory failure the latter resulting from a decrease in blood volume as a consequence of an increase in systemic capillary permeability. They both noted that the falling blood pressure at the height of the illness coincided with the appearance of edema and with a fall in the concentration of serum proteins, particularly albumin.

In a more detailed investigation of the pathophysiology of the peripheral circulatory failure in RMSF, Harrell in 1949 reported serial observations in 13 patients.¹⁸ The entire natural history of the illness was observed since neither tetracycline nor chloramphenicol was then available as specific treatment. Sequential measurements of plasma volume (using Evans Blue dye), extravascular volume (using thiocyanate space) and the serum concentrations of total protein, albumin, nonprotein nitrogen (NPN) and chloride were correlated with various clinical observations and the effect of intravenous therapy with crystalloid and colloid containing solutions was noted. The illness was considered mild if the tourniquet test was negative, there was no edema and the pulse and blood pressure were stable; moderate if the tourniquet test was positive, there was slight edema, the pulse rate was increased and the patient appeared toxic and severe if there were purpura, marked edema and delirium. Cases with a fulminant clinical course were not included. Data were summarized for the moderate to severe cases at three stages: (1) soon after

Table 1

| Disease | Etiology | Vector | Geographic distribution |
|--|-------------------------|----------------------------------|---|
| Typhus group | | | |
| Epidemic typhus | <i>R. prowazeki</i> | Louse | Historic, all continents except Australia Recent: Burundi, Rwanda, Uganda, Ethiopia, Algeria, Chad, Niger, Zambia, Nigeria, Zaire, Liberia, Bolivia, Peru, Ecuador, Chile, Guatemala, Costa Rica, Mexico |
| | | Ectoparasite of flying squirrels | Southeastern U.S. |
| Recrudescent typhus | <i>R. prowazeki</i> | None | Worldwide, especially localities of previous typhus epidemics, e.g., Poland and Yugoslavia, or countries of immigration of previous typhus cases, e.g., U.S. and Canada |
| Murine typhus | <i>R. mooseri</i> | Rat flea | Worldwide, especially in warmer climates including U.S. |
| Spotted Fever group | | | |
| Rocky Mountain spotted fever | <i>R. rickettsii</i> | Tick | U.S., especially southeastern states, western Canada, Brazil, Colombia, Mexico, Panama |
| Old world tick-borne spotted fever (Boutonneuse fever) | <i>R. conorii</i> | Tick | Mediterranean basin, Africa, Asia |
| South African tick bite fever, Kenya typhus, etc. | | | |
| Siberian tick typhus | <i>R. sibirica</i> | Tick | Siberia |
| Queensland tick typhus | <i>R. australis</i> | Tick | Australia |
| Rickettsialpox | <i>R. akari</i> | Mite | Probably worldwide, documented in cities of U.S. and U.S.S.R. |
| Central European tick typhus | <i>R. slovaca</i> | Tick | Central Europe, Armenia |
| Scrub Typhus group | | | |
| Scrub typhus | <i>R. tsutsugamushi</i> | Mite | Eastern and southern Asia and southwestern Pacific |

states, however, there is a higher incidence in the southeastern states with North Carolina, Virginia, Tennessee, Oklahoma, South Carolina, Georgia, and Maryland reporting 66.1% of all cases between 1975 and 1977. Cases occur most often in children in males and between mid-April and mid-September. Moreover, mortality rates are higher for adults (over age 30: 13.9% vs. 4% under age 30), males (8.2% vs. 4.5% in females), and nonwhites (13.9% vs. 5.8% in whites).⁴ Fatal cases seek medical attention at the same time during the course of illness as nonfatal cases. However, their rash appears later, they give a history of tick bite less often or later in the course, and initial or unexpected symptoms lead to misdiagnosis. As a result of incorrect or delayed diagnosis, antirickettsial treatment is not given or is given too late to be effective.⁷

⁴ Effect of rickettsiae on the microcirculation. Dermal involvement in rickettsial diseases is not only a prominent clinical sign but also an opportunity to observe and evaluate the nature of the

vascular events. The observations indicate that the microcirculation is the primary target with variable subsequent contiguous centripetal extension to arteries and veins. The temporal sequence of events which may be seen in the skin of patients with typhus and RMSF reflects the pathologic and pathophysiologic events in these diseases.

The rash of RMSF is delayed, usually occurring three days after onset of fever with a range of 2 to 7 days and rarely not appearing at all.⁸⁻¹¹ The rash tends to appear first on ankles, feet, wrists, and hands, and to spread centripetally to involve the entire body within 24 to 36 hours, usually including the palms and soles. This centripetal spread contrasts with the centrifugal spread of the rash of typhus. The difference has never been satisfactorily explained, although optimal growth of *Rickettsia rickettsii* at lower temperatures¹² would favor earlier attainment of a critical mass of pathogenic organisms in peripheral sites. Initially, the rash consists of pink, unelevated

strated in the only case of fulminant RMSF with description of pathology reported in the literature.² In our case study of serial sections stained for fibrin histochemically and for *Rickettsia rickettsii* immunohistochemically demonstrated that thrombotic glomeruli were intensely infected and that nonthrombotic glomeruli were minimally or mildly infected. In an intermediate position, several recent cases with death occurring on day 6 or 7 of disease have had rare focal glomerular thrombi. These observations on thrombosis in renal tissue from rickettsial diseases indicate that thrombosis is the response to local injury to blood vessels by rickettsiae.

Two lesions which could be due to local and/or systemic effect of rickettsial infections are glomerulonephritis and edema of the kidneys. There is no consensus that glomerulonephritis actually occurs in rickettsial diseases. Glomerulonephritis was described by Allen and Spitz²³ in scrub typhus and RMSF. Ultrastructural examination of renal biopsies from five Brazilian cases of RMSF with various degrees of acute renal functional impairment demonstrated no glomerulonephritis with only nonspecific endothelial swelling and prominence of mesangial cells.²⁴ Our cases when studied by sections with controlled thickness (3 μ m) and staining of basement membranes revealed no glomerulonephritis as judged by the absence of glomerular hypercellularity and basement membrane lesions. Another recent study²⁵ has shown no glomerular immune complexes by immunofluorescence and no ultrastructural deposits. On the other hand increased renal weights, presumably secondary to edema have been reported in some cases of scrub typhus²⁶ and RMSF.¹ This edema may result from multifocal vasculitis and/or acute tubular necrosis.

The significant pathologic lesion which is the effect of systemic shock on the kidneys is acute tubular necrosis (ATN). In two of 37 cases of typhus fever heavy kidneys with pale bulging cortices were compatible grossly with ATN.²⁶ Although ATN is not always identifiable morphologically in all of its time course and autolysis often renders tubular epithelium impossible to evaluate microscopically, the stage of ATN identifiable by markedly thin tubular epithelium and interstitial edema has been reported in cases of RMSF.^{27,28}

Renal pathophysiology in rickettsial diseases
With reference to humoral and cellular

function the remote effects of the systemic vasculitis far outweigh the effects of the observed intrarenal pathology and can best be understood as the sequential manifestations of altered systemic capillary permeability.²⁹ Interesting in the basic renal lesion, a focal perivascular interstitial nephritis, finds little clinical expression. Early in the course of the more severe rickettsial infections, patients often present with dehydration, a moderately elevated BUN and serum creatinine concentration, mild hyponatremia and hypoproteinemia, a low normal blood pressure and progressive hypovolemia. The BUN is often high in relation to the serum creatinine concentration, and the urine volume is reduced though usually not to oliguric levels. There is a trace to 1+ proteinuria by reagent stick and 24 hour collections contain less than 500 mg of protein. The urine sediment contains a few coarsely granular casts but no increase in cellular elements. The urine specific gravity is usually greater than 1.010 and urine sodium concentration is low, often less than 10 mEq/L. Expansion of intravascular volume with colloid or crystalloid solutions restores renal function to normal within a few days. This entire picture is consistent with prerenal azotemia.

At the height of illness in severe cases with a more protracted course acute hypotension may precipitate oliguric acute renal failure (ATN). Despite prompt restoration of blood pressure to normal and maintenance of intravascular volume the oliguria persists. The urine composition and sediment are typical of ATN. Recovery from ATN, in this setting has been reported in boutonneuse fever, a milder but related rickettsial infection³⁰ but not to date in Rocky Mountain spotted fever, although the potential for recovery has been demonstrated. Oliguric acute renal failure is a regular occurrence in fulminant cases, in association with systemic circulatory collapse. Causes other than hypotension have been considered in the pathogenesis of ATN in Rocky Mountain spotted fever specifically non traumatic rhabdomyolysis with myoglobinuria but evidence to support their occurrence is lacking.

As noted histologic lesions of acute glomerulonephritis were described in one early report of RMSF. A review of published cases and our own material however, does not reveal adequate documentation of this lesion and there is no clinical data (heavy proteinuria, hematuria

onset of the rash (2) at the height of illness 9 to 14 days after onset of the rash and (3) during the recovery period in the third week after onset of the rash

Patients presented shortly after the appearance of the rash with clinical signs of dehydration an elevated NPN and low serum chloride concentration a normal or slightly low serum protein concentration and plasma volume a normal thiocyanate space and a low normal blood pressure. When intravenous therapy with crystalloid solutions was given in an effort to correct the dehydration at this point in the illness there was a prompt fall in the NPN and a rise in serum chloride concentration. Plasma volume rose transiently and there was a reciprocal fall in the serum protein concentration. If crystalloid solutions were continued the expansion of plasma volume was sustained and there was a striking rise in the thiocyanate space coinciding with the development of progressive peripheral edema.

At the height of the illness the onset of hypotension was associated with a more marked reduction in the serum protein concentration and plasma volume elevated thiocyanate space and peripheral edema. Crystalloid administration at this point accelerated the extravascular accumulation of fluid without a favorable effect on the blood pressure or plasma volume.

The onset of recovery was marked by return of temperature to normal and a reversal of the above abnormalities. The blood pressure rose to normal as plasma volume began to increase. The thiocyanate space gradually decreased as edema was mobilized and diuresed and finally the serum protein concentration returned to normal. The administration of colloid solutions such as plasma or albumin in contrast to crystalloids did support the blood pressure and plasma volume at the height of illness and early in the recovery period but in five of the six instances reported its administration also precipitated acute pulmonary edema. These findings were interpreted to indicate that the vasculitis of RMSF led to a progressive increase in systemic capillary permeability such that there was a gradual loss of protein from the vascular compartment and a decrease in intravascular oncotic pressure. Although this study served to characterize the sequential changes in systemic capillary permeability in the more severe cases it left unanswered important questions about fluid therapy and also raised

basic questions about cardiac function and pulmonary capillary function in RMSF.

Renal pathology in rickettsial diseases. The pathologic lesions of kidneys in rickettsial diseases may be considered to be either of two types lesions due to local effects of rickettsiae on renal vessels or lesions due to the effects of systemic hypovolemic shock. In studies of typhus fever Wolbach described focal lesions in which only small blood vessels are affected and the cellular response is infiltrative. These lesions contained capillaries or precapillary blood vessels surrounded by mononuclear phagocytes lymphocytes plasma cells and polymorphonuclear leukocytes and incorporated one or several tubules in various stages of injury up to actual necrosis. Wolbach noted that these lesions were present also in scrub typhus and Rocky Mountain spotted fever but that in all three diseases the distribution was spotty and little renal parenchyma was involved. In the classic description of the pathology of RMSF Lillie observed that 12 of 17 cases had focal lesions with irregular interstitial and perivascular infiltration by lymphocytes in later cases often plasma cells and large lymphoid cells as well. These lesions were especially marked at the corticomedullary junction. Focal pericapillary and interstitial hemorrhages were identified in six cases. Our study confirmed these observations and demonstrated by specific immunofluorescence that the distribution of the majority of the *Rickettsia rickettsii* was identical with that of the multifocal perivascular interstitial nephritis concentrated near the corticomedullary junction.²²

Another potential local effect of rickettsial infection on the kidney is thrombosis. Wolbach described precisely this relationship in typhus fever with thrombosis of vessels in the focal interstitial lesions no lesions of large blood vessels and one case with small mural thrombi in small arteries of the pyloric submucosa with rickettsiae in the endothelium of the affected vessels.²³ Our original study of ten cases of RMSF with histochemical staining for fibrin revealed thrombi only in vessels of a minority of the focal interstitial lesions and no glomerular thrombi.²⁰ Subsequently we have investigated a case of fulminant RMSF (defined by Parker¹ as fatal within 3 to 5 days of onset) which showed fibrin thrombi in approximately half of the glomeruli. Glomerular fibrin thrombi were also demon-

nine cases.³ Absence of left ventricular dilatation indicated that severe myocardial failure was not the etiology of hypotension, shock, and death in these cases of RMSF.

Pathologic studies of lung in rickettsial disease have demonstrated interstitial pneumonitis with alveolar walls containing mononuclear leukocytic infiltration.^{14, 18, 19, 23, 26, 28, 33} In cases which were not complicated by bronchopneumonia, interstitial pneumonitis was manifested grossly by congestion and edema. Further microscopic evidence for loss of vascular integrity are multiple foci of alveolar hemorrhage, fibrin, and edema. Examination of lungs from cases of RMSF by specific immunofluorescence has revealed moderate to severe infection of the pulmonary microcirculation by *Rickettsia rickettsii* (see illustrative Case 2 below) thus providing a pathogenetic explanation for the interstitial pneumonitis and the increased pulmonary vascular permeability.³³

Cardiovascular and pulmonary pathophysiology in rickettsial diseases. The studies already referred to convincingly exclude any significant contribution by the heart to the development of hypotension and peripheral circulatory collapse in the course of severe rickettsial infection, but the role of the heart in the development of pulmonary edema, a less common complication, has been more difficult to clarify. In his classic study of the typhus heart, Woodward documented the fact that central circulatory failure and pulmonary edema were distinctly uncommon. None of the 30 severely or critically ill patients he studied during the course of their illness had cardiac enlargement by physical examination, a gallop rhythm, distended neck veins, or an enlarged liver. He recorded serial measurement of venous pressure. Values above 12 cm water were not seen, and the average value was 8 cm water. Radiographs were available in 12 patients and showed neither cardiomegaly nor pulmonary congestion. Electrocardiograms showed no striking deviations from normal. Rales were heard frequently, but usually in association with coarse rhonchi and were considered to be manifestations of tracheobronchitis or patchy bronchopneumonia, both of which were often observed at necropsy.

Pulmonary edema has usually been noted in scrub typhus in conjunction with other findings of severe disease. In the critically ill patients, the pulmonary

edema was considered to be a manifestation of severe rickettsial pneumonitis.⁴

Pulmonary edema has been most frequently reported in RMSF and its pathogenesis is of critical importance with regard to fluid management. A careful review of the case reports of the 13 patients Harrell originally described in his study of peripheral circulatory failure revealed that five developed pulmonary edema during the course of their illness.¹⁷ The episodes of pulmonary edema all occurred in the second week of illness, at the height of the changes in systemic capillary permeability, or a few days into the recovery period. The administration of solution containing colloid immediately preceded the development of pulmonary edema in three instances and an increase in plasma volume was documented by the Evans Blue dye. Distended neck veins were not observed however, and the one recording of venous pressure during an episode of pulmonary edema revealed a value of 10 cm H₂O. A gallop rhythm was noted in one instance. Treatment consisted of diuresis, administration and fluid restriction. There was clinical resolution of the pulmonary edema in 48 hours in four of the patients, but the fifth patient developed bacterial pneumonia and died.

A recent clinical study of the pulmonary manifestations in RMSF confirms and extends the observations.³⁴ The records of all patients hospitalized and documented to have RMSF between 1973 and 1976 were reviewed. Nine of the patients had deterioration in pulmonary function during the first week of hospitalization with widening of the alveolar arterial oxygen difference. Seven developed radiographic infiltrates and six developed pulmonary edema. All were in markedly positive fluid balance and had received large amounts of fluid following hypotensive episodes. None of the patients had third heart sounds, cardiac enlargement radiographically or electrocardiographic changes. Of the patients with severe disease, death within 48 hours of hospitalization. Diuresis in the other eight patients led to prompt improvement of pulmonary edema cleared within 48 hours.

Since 1976 we have seen two additional cases which illustrate the clinical presentation of pulmonary involvement in RMSF and the changes which highlights the pathological changes.

red cell casts) to support the occurrence of acute glomerulonephritis

Thus the major clinical abnormalities in renal function prerenal azotemia and ATN are the early or later consequences of the systemic vasculitis. Recovery of renal function with prerenal azotemia is the rule and the potential for recovery from ATN with resolution of the vasculitis is suggested.

Cardiovascular and pulmonary pathology in rickettsial diseases. In general the heart in typhus fever RMSF and scrub typhus manifests negligible gross alterations and virtually universal microscopic interstitial mononuclear myocarditis. Wolbach felt that inflammatory infiltration of the myocardium was diffuse because of its relationship to the most diffusely distributed blood vessels the capillaries that the order of seventy of inflammatory infiltration was scrub typhus typhus and RMSF and that not much evidence of degeneration of heart muscle could be demonstrated.¹¹ Myocarditis was noted in a series of eight autopsies of cases of RMSF by Wilson and Chowning in 1904.¹² They noted a few epicardial petechiae dark fluid blood filling the right ventricle empty left ventricle and considerable round cell infiltration. Following a number of case reports by a series of authors often citing myocarditis Lillie published the classic description of myocarditis in RMSF in his series of 17 cases.¹³ Grossly he noted that the right ventricle was more often dilated than the left but in the majority the status of the chambers was normal or contracted and that altogether gross changes were slight. Microscopically two cases were normal 15 manifested interstitial infiltration of variable density chiefly by lymphocytes often with lesser numbers of plasma cells monocytes a few neutrophil or eosinophil leukocytes or mast cells. Myocarditis was irregular and patchy often distinctly centered about small vessels and in interfascicular connective tissue. Only two cases had focal coagulative necrosis of myocardial cells.

In the definitive study of the pathology of typhus Wolbach stated that as a rule the left ventricle was contracted and the right moderate to dilated.¹⁴ In six postmortem examinations performed soon after death in cases without significant bacterial complications myocardium showed pallor loss of consistency and yellowish streaks and points. Acute valvular lesions and

macroscopic mural thrombi were not detected. Microscopic lesions which were observed in all 37 necropsies included slight degrees of edema focal and diffuse myocarditis with interstitial macrophages lymphocytes plasma cells few polymorphonuclear leukocytes and vascular lesions almost wholly restricted to capillaries and vessels of pre capillary size. Large blood vessels in the heart and pericardium very rarely contained lesions. Pathologic studies of the heart in scrub typhus have yielded essentially the same observations as in typhus fever and RMSF.¹⁵

Besides myocarditis there have been few consistent pathologic alterations of the heart in the rickettsial diseases. When present they have included few subendocardial mononuclear inflammatory foci pericardial fluid varying from none to moderate to rarely large amounts and an occasionally demonstrated focal inflammatory lesion involving a conduction bundle¹⁶ or the Purkinje conduction system.

The relationship of rickettsiae to the myocarditis has been unclear. Much of this unsatisfactory state has been a result of the unreliability of the various Giemsa techniques to demonstrate rickettsiae. Even in the hands of Wolbach who used the method to demonstrate rickettsiae successfully in many lesions of typhus and spotted fever rickettsiae could not be satisfactorily demonstrated in heart lesions of typhus fever. Of 40 cases of RMSF in which Giemsa stain was reported to have been used to search for rickettsiae in heart only a single case was reported to contain rickettsiae within the cytoplasm of the endothelial cells of the subepicardial and interstitial capillaries.¹⁷ In contrast *Rickettsia rickettsii* were demonstrated in hearts of all eight untreated or inadequately treated cases of RMSF which were examined by a technique of deparaffinization trypsin digestion and specific direct immunofluorescence in our laboratory.¹⁸

Rickettsia rickettsii were observed in capillaries venules arterioles and large vessels including coronary arteries in descending order of involvement. Vascular infection with resultant vascular injury and increased permeability provides the probable pathogenetic mechanism for moderate myocardial edema. Data on the same series of hearts with etiologically confirmed RMSF which suggested myocardial edema were increased heart weight in eight of nine cases and detectably increased interstitial volume in six of

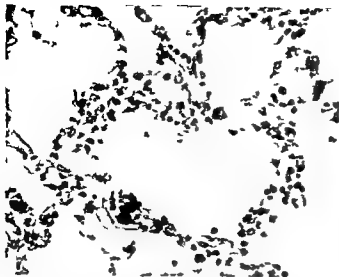


Fig 2 Photomicrograph of lung from Case 2 of RMSF. Interstitial pneumonia is characterized by mononuclear cell infiltration of the alveolar septa. Proteinaceous edema fluid fills the alveolar spaces (Hematoxylin-eosin stain, original magnification $\times 220$).



Fig 3 Photomicrograph of lung from Case 9 of RMSF. Brightly immunofluorescent *Rickettsia rickettsii* are visible within thickened portions of an alveolar septum (Fluorescein isothiocyanate conjugated anti-*Rickettsia rickettsii* globulin fraction, original magnification $\times 340$).

respiratory infection was diagnosed and treated symptomatically. Over the next two days she developed nausea, vomiting, high fever, and malaise. Physical examination at the time of admission showed a blood pressure 80/60 mm. Hg and a pulse rate of 100 beats per minute. She was oriented though lethargic and appeared acutely ill. Physical examination showed no rash. Scleral icterus was noted but without enlargement or tenderness of the liver. The lungs were clear to auscultation and no signs of heart failure were observed. Liver function tests were markedly abnormal with total bilirubin 15 mg/dl, moderately elevated alkaline phosphatase, and markedly elevated liver enzyme values. The BUN was 91 mg/dl and serum creatinine was 4.8 mg/dl. The serum sodium was 125 mEq/L, serum calcium 6.8 mg/dl, total protein 5.8 g/dl, and albumin 3.1 g/dl. Febrile agglutinins included a Proteus OX 19 titer of 1:20. Fluids were given as 5% dextrose in water alternating with normal saline at a rate of 3000 ml per day and methylprednisolone was given intravenously 1 gm every 8 hours. The blood pressures rose initially but she remained oliguric and her general condition deteriorated. Thirty-six hours after admission therapy with tetracycline was begun intravenously 500 mg every 8 hours. Forty-six hours after admission the patient became intubated and hypotensive. Two hours later a cardiorespiratory arrest

occurred following an episode of vomiting; the patient could not be resuscitated.

Pertinent necropsy findings were multifocal interstitial pneumonitis, bilateral pulmonary edema (Fig 2) associated with severe rickettsial infection of alveolar capillaries (Fig 3), mild mononuclear interstitial myocarditis, and acinar tubular necrosis with cortical interstitial edema and low regenerative tubular epithelium.

Comment. Although lacking extensive pulmonary clinical and functional data, this patient is an excellent example of the pathologic and etiologic involvement of lungs, heart, and kidneys in RMSF. Despite initiation of tetracycline treatment on her fourth day of illness, she succumbed to a severe rickettsial infection. As suggested clinically by the persistent oliguria following restoration of blood pressure to normal with intravenous fluids, she had acute tubular necrosis at autopsy. One of the most important manifestations of her disease was severe rickettsial infection of the pulmonary microcirculation with alveolar edema. Pulmonary edema was documented grossly and microscopically in the face of only mild mononuclear interstitial myocarditis.

Based on the pathological changes we have described in the heart and lungs and the clinical data referred to above, it appears that the pulmonary edema seen in RMSF is most

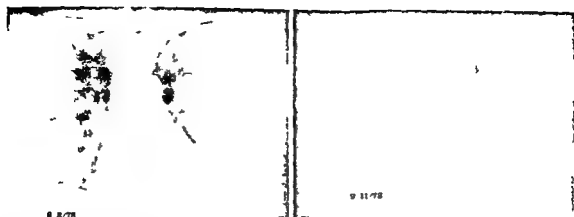


Fig 1 Chest radiographs in Case 1 of RMSF. On the left admission (left) heart size and pulmonary vascular pattern are normal. After two days of parenteral fluid administration (right) heart size is unchanged but radiologic pattern of pulmonary edema is present.

Illustrative cases

Case 1 A 48 year old white housewife from Smithfield N C removed a tick from her scalp 7 days before admission. Three days later she developed severe headache, nausea and fever. Hereafter she had daily fevers of 40 C and intermittent vomiting. Three days before admission a red macular rash was noted on the trunk and extremities including the palms and soles. She was admitted to North Carolina Memorial Hospital on September 8, 1978. Physical examination showed a blood pressure of 140/80 mm Hg and a temperature of 40 C. Pulse rate was 100 beats per minute. She was oriented and alert but appeared weak and acutely ill. A generalized maculopapular rash with petechial areas was noted on the trunk and extremities. The lungs were clear, the neck veins were not distended and examination of the heart showed no enlargement or gallop rhythm. There was no peripheral edema or adenopathy and the neurological examination was normal. Blood chemistries included sodium 133 mEq/L, BUN 15 mg/dl, creatinine 0.8 mg/dl, calcium 8.6 mg/dl, total protein 6.5 g/dl, and albumin 3.5 g/dl. The hematocrit was 37% and the platelet count 92,000/ μ l. The prothrombin time and partial thromboplastin times were normal. The initial chest radiograph (Fig 1) was interpreted as normal. A skin biopsy on the day of admission examined by specific direct immunofluorescence was diagnostic for Rocky Mountain spotted fever with *Rickettsia rickettsii* in dermal blood vessels.

She was begun on treatment with intravenous chloramphenicol 100 mg every 8 hours and

intravenous hydration with 5% dextrose in normal saline at a rate of 75 ml/hr. On the second day after admission she developed progressive shortness of breath over a period of several hours. Examination revealed diffuse rales but the neck veins were not distended and no gallop rhythm was heard. The blood pressure was 160/80 mm Hg. Arterial blood gases revealed pH 7.52, P_{CO_2} 22 torr and PO_2 30 torr. Repeat serum total protein was 6.5 g/dl with albumin 3.0 g/dl. The electrocardiogram showed sinus tachycardia and non-specific ST segment changes. A repeat chest radiograph was interpreted as showing pulmonary edema (Fig 1). She was transferred to the intensive care unit where she was treated with oxygen, furosemide and digoxin. Within three days pulmonary gas exchange had improved and the rales and pulmonary infiltrate on chest radiograph had cleared. Her recovery was uneventful.

Comment Fluid administration in this otherwise stable patient led to the abrupt development of pulmonary edema in the absence of signs of heart failure or elevated systemic venous pressure. The predominance of infiltrates in the upper lobes is similar to that seen when pulmonary capillary wedge pressure is elevated—i.e. in cardiogenic pulmonary edema—but might have occurred at only slightly increased pulmonary capillary wedge pressure in the presence of both a decreased intravascular oncotic pressure and altered pulmonary capillary permeability.

Case 2 A 19 year old black female from Rock Hill S C was seen by her physician two days prior to hospitalization at which time an upper

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non cardiogenic. It typically occurs after vigorous fluid administration usually at the height of illness and is probably a consequence of an increase in pulmonary capillary permeability. Confirmation of the pathogenesis of the pulmonary edema however will require more specific physiologic data including measurements of pulmonary capillary wedge pressures, pulmonary capillary oncotic pressures and pulmonary interstitial oncotic pressures as estimated by the measurement of edema fluid protein concentration.²

Conclusions

The documented changes in systemic capillary permeability and probable changes in pulmonary capillary permeability which we have discussed have definite therapeutic implications with reference to intravenous fluid therapy in severely affected patients. The selection of fluids either colloids or crystalloids is particularly controversial in terms of predicting the effect on the Starling forces in the pulmonary circulation.

The use of crystalloids may cause both a small increase in intravascular hydrostatic pressure (PCWP) and by dilution a small decrease in intravascular oncotic pressure. The net change in filtration pressure may be sufficient to favor transudation of fluid into the pulmonary interstitium. Colloid administration may cause an increase in pulmonary intravascular hydrostatic and oncotic pressures but interstitial oncotic pressure may also rise if pulmonary capillary permeability to proteins is sufficiently altered favoring the development of pulmonary edema.

As noted five of the 13 patients reported by Harrell developed pulmonary edema after colloid was administered at the height of the illness.

Among the conclusions that can be reached with certainty is the fact that pulmonary function is particularly at risk in severe RMSF. Patchy areas of vasculitis and interstitial edema in the kidney or heart may cause little damage to renal tubular transport or myocardial contraction and in the systemic circulation may not impair flow or peripheral delivery of nutrients (at least until hypotension supervenes). These same pathologic changes in the pulmonary capillaries on the other hand may lead to an acute increase in lung water and impairment of gas exchange.

The purpose of fluid administration in severe

rickettsial infections is to expand intravascular volume and support blood pressure so that adequate perfusion of vital organs and peripheral tissues can be maintained during the acute phase of the vasculitis. Care should be exercised to limit fluid administration (1) to avoid the accumulation of peripheral edema with the attendant risk of subsequent intravascular volume overload as vascular integrity is restored and (2) to minimize the risk of developing pulmonary edema particularly at the height of the illness when pulmonary capillary permeability may be significantly increased. Monitoring of pressures in the pulmonary capillary circulation should be considered in the severely ill patient with hypotension to assist in the selection and use of intravenous fluids.

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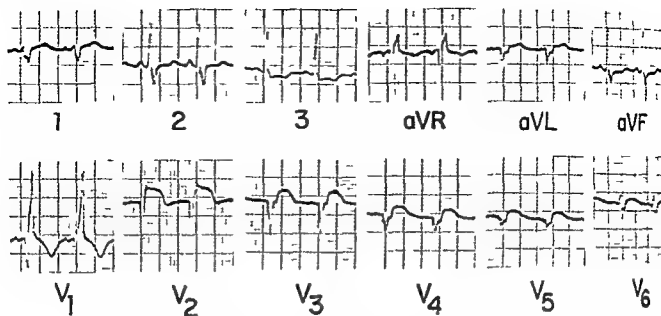


Fig 1 Electrocardiogram on admission with sinus rhythm, right axis deviation, right bundle branch block, and pathologic Q waves with ST elevation in Leads I, L, and V to V₆.

positive for MB fraction. Swan Ganz catheterization showed a cardiac output of 4.6 liters/minute, a cardiac index 3.11/min/M², and a pulmonary capillary wedge pressure of 18. Over the first three days in hospital, she also developed bibasilar rales, an increase in heart size by radiograph, and a rise in her pulmonary capillary wedge pressure to 30. Her pericardial friction rub resolved by 48 hours. She was treated with digoxin and furosemide and continued on aspirin for pericarditis and fever.

Other laboratory studies showed an elevated sedimentation rate (62 mm by the Wintrobe method), a negative rheumatoid factor, and lupus erythematosus preparations, normal serum protein electrophoresis, and immunoglobulin C3 and C4, and an antinuclear antibody titer of 1:80. Thallium myocardial perfusion imaging revealed anteroseptal and apical defects. Gated blood pool scan showed little or no motion of the anterior wall and an ejection fraction of 35%. No pericardial effusion was noted on the echocardiogram. Over a seven-day period, her ECG showed loss of R waves anteriorly and a resolution of the ST changes.

On the eleventh hospital day, cardiac catheterization was performed. Coronary angiography showed a normal left main coronary artery and a proximal left anterior descending coronary artery which was totally occluded in its proximal course. There was some left to left collateral filling at the

distal LAD. The remainder of the coronary tree was entirely normal (Fig 2). A left ventriculogram done in the RAO and LAO projections showed a mildly dilated left ventricular chamber, mitral regurgitation, fair overall contractility, but an akinetic segment involving mid anterior wall apex and the distal inferior wall (Fig 3). Left ventricular end-diastolic volume was 123 ml, stroke volume was 32 ml, and calculated ejection fraction was 26%. Left ventricular end-diastolic pressure after contrast injection was 30 mm Hg. Bundle studies showed a normal A-H and H-V time.

Post hospital course

DR. DAVID BLUMENTHAL: The patient's subsequent recovery was uneventful, and she was discharged on digoxin 0.25 mg per day. One month later, she was admitted to evaluate her anterior chest pain, similar to that experienced with the prior acute infarction. At that time, she had a diffusely palpable point of maximal impulse, a right pleural effusion, bibasilar rales, and mild hepatomegaly. Her electrocardiogram was unchanged. Six days after admission, she was discovered unresponsive, pulseless, apneic, and in ventricular fibrillation. Immediate cardiopulmonary resuscitation was initiated and was successful. The subsequent hospital course was complicated by ventricular tachycardia, which

Clinical pathologic conference

Delayed acute myocardial infarction after blunt chest trauma in a young woman

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Case presentation

DR KIM FEHR The patient was a 25 year old woman who was in entirely good health until five days before presenting to hospital when she was involved in an automobile accident in which her car was thrown into a spin and she struck her forehead and chest on the steering wheel. She was treated in a nearby hospital emergency room for local chest bruising and tenderness. Chest and skull radiographs were normal. Mild dyspnea on exertion developed at home and five days post trauma when she suddenly developed a persistent squeezing substernal chest pain accompanied by nausea vomiting and cold diaphoresis. After 24 hours of pain she presented to the hospital complaining of substernal chest pain and also sharper pain aggravated by breathing.

Her past medical history was remarkable for a five year history of heroin abuse for which she was taking methadone. She was on no other medication had never taken oral contraceptives and was not recently pregnant. Her only cardiovascular risk factor was a 24 pack year history of smoking.

Initial physical examination revealed a moder-

ately distressed young woman complaining of chest pain. Pertinent physical findings included a blood pressure of 130/80 mm Hg without pulsus paradoxus, a regular pulse of 96 and normal respirations. Her chest wall showed no local bruising or tenderness. Her lungs were clear without rales rhonchi rales or wheezes. On cardiac examination the point of maximal impulse was in the fifth intercostal space midclavicular line. Her heart sounds were normal, a soft ventricular gallop (S₃) and a pericardial friction rub was present. There were no murmurs, thrills, carotid bruits, jugular venous distention, hepatojugular reflux, hepatosplenomegaly, cyanosis, clubbing or peripheral edema.

The chest radiograph showed a normal cardiac silhouette with a cardiothoracic ratio of 12/25. The electrocardiogram (Fig 1) showed normal sinus rhythm, right axis deviation, right bundle branch block and pathologic Q waves with ST elevation in Leads I, L and V₁ to V₄, compatible with an acute anterior wall myocardial infarction. Her initial creatine kinase (IU) was 2,390 and the remainder of her laboratory findings were unremarkable.

Hospital course

DR DOLORES SHOBACK Her hospital course was initially complicated by the development of complete heart block requiring a transvenous pacemaker for a period of five days after which normal sinus rhythm returned. Creatine phosphokinase (CK) every four hours showed subsequent values of 2,080, 1,930, 1,760, 650 and 588 which

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Table I

| Author date | Patient | | Etiology of blunt trauma | Coronary artery involved | ECG |
|-----------------------|---------|-----|---|--------------------------|---|
| | Age | Sex | | | |
| Warburg 1940 | 59 | M | Run over by bicycle fell on chest | LAD | |
| MacDonald 1941 | 21 | M | Struck in chest by softball | LAD | |
| Jokl et al 1944 | 10 | M | Struck in chest during boxing match | LAD | |
| Hedinger 1948 | 53 | M | Kicked in chest by horse with fracture of sternum | LAD | |
| Levy 1949 | 49 | F | Auto accident struck chest on front seat | LAD | Anteroseptal MI |
| Lehmus et al 1953 | 62 | M | Auto accident struck chest on dashboard | LAD | |
| Stewart 1967 | 42 | M | Struck by piece of wood recoiling from circular saw | LCfx | Posterolateral MI subsequent development RBBB |
| Harthorne 1967 | 32 | M | Struck in chest during barroom brawl | RCA | Inferior wall MI |
| Heyndrickx et al 1974 | 62 | M | Auto accident struck chest | RCA | Inferior wall MI complete heart block |
| Stern et al 1974 | 16 | M | Auto accident struck chest on steering wheel | LAD | RBBB anterior wall MI |
| Oren et al 1976 | 35 | M | Struck in chest by fist | LCfx | Inferior and posterior MI |
| de Feyter et al 1977 | 36 | M | Struck in chest by football | LAD | Anterior wall MI |
| Candell et al 1979 | 38 | M | Auto accident struck chest | LAD | Anteroseptal MI left axis deviation |
| | 44 | M | Auto accident struck chest | RCA | Inferior wall MI complete heart block |
| Oliva et al 1979 | 17 | F | Auto accident struck chest on steering wheel | RCA | Inferior wall MI |
| Present Case | 25 | F | Auto accident struck chest on steering wheel | LAD | RBBB anterior wall MI |

Abbreviations: F = female; LAD = left anterior descending coronary artery; M = male; MI = myocardial infarction; RBBB = right bundle branch block; RCA = right coronary artery.

ventricular pacing failed to elicit ventricular tachycardia.

Five months after the original infarction the patient died suddenly while driving an automobile. On her prior clinic visit she claimed to have taken her digoxin and procainamide faithfully.

Clinical discussion

DR STEPHEN VLAY It is likely that this young woman's myocardial infarction was somehow related to the chest trauma which occurred one week before her occlusion. Nonpenetrating trauma

to the chest may injure almost any portion of the heart resulting in myocardial contusion, aneurysm or rupture. There may be pericardial injury or the trauma may bring about valvular dysfunction due to laceration or rupture of the valves. Occlusion of a major coronary artery as a direct result of blunt trauma has been regarded as rare, and has been reported only in the presence of preexistent coronary artery disease. In their series of 546 autopsy cases of nonpenetrating cardiac trauma, Parmley and colleagues¹ reported no instances of coronary occlusion although they



Fig 2 *Left* In the right anterior oblique (RAO) projection the left anterior descending coronary artery is occluded proximally (arrow) immediately after the takeoff of the first LAD diagonal branch. The left circumflex system is normal. *Right* The RCA system is free of disease.

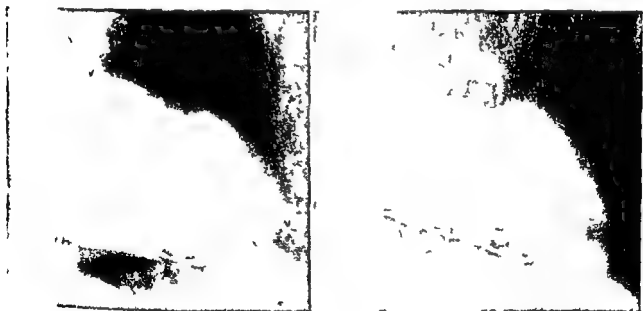


Fig 3 The left ventriculogram in the RAO projection is shown in diastole (*left*) and systole (*right*). Marked thickness of the anterior wall, apex, and distal inferior wall is demonstrated with preservation of function in the proximal inferior wall.

sponded poorly to intravenous lidocaine and was exacerbated by oral quinidine. Intravenous procainamide abolished the dysrhythmia and an oral preparation was substituted. An electrophysiologic study to assess the degree of ventricular

irritability was undertaken with the patient receiving procainamide and demonstrating therapeutic serum levels. Four sites in the ventricle studied for the repetitive ventricular response during sinus rhythm and two sites studied during

allels that reported by Stern and associates¹ in which a young man in his 30s sustained an anterior myocardial infarction after an auto accident and at angiography was found to have complete occlusion of the proximal LAD with otherwise normal coronary arteries. In both reports there were no apparent risk factors of coronary occlusion and no evidence of connective tissue disease.

DR BLUMENTHAL The severity of chest wall trauma does not appear to correlate with the occurrence of coronary occlusion following trauma as was seen in our patient.³ An elastic compressible nonfracturing rib cage may result in more severe cardiac damage than one that fractures and dissipates mechanical energy.^{2,11} Many of the cases^{1,2,12} however were associated with local ecchymoses or rib fractures. The most violent injury was an auto accident reported by Heyndrickx and colleagues¹¹ in which a patient suffered major trauma to the thoracic cage and sustained rupture of the right coronary artery.

DR BERNADINE BULKLEY The etiology of myocardial infarction due to nonpenetrating chest injury is not entirely clear. Studies in the previously reported cases suggest varied etiologies: (1) atherosclerotic heart disease either diffuse or isolated complicated by hemorrhage into a plaque or spasm; (2) coronary thrombosis due to direct vascular trauma; (3) spasm in normal coronary arteries; (4) frank rupture of the vessel; (5) dissecting aneurysm; and (6) coronary embolization. The presence of coexisting coronary artery disease has been raised by some as a necessary predisposing factor. In the 16 cases under analysis however only four had evidence of extensive atherosclerotic disease. Another four were described as having slight or insignificant lesions. Unfortunately in some of the earlier cases the degree of obstruction was not quantitated. How important a role slight or insignificant lesions may have played in the subsequent myocardial infarction remains a matter of speculation. Of cases without other lesion eight were documented by angiography. Thus in the small group of patients preexisting coronary artery disease was not a mechanism for the induction of coronary occlusion following trauma.

Patients with atherosclerotic disease however may be at a greater risk for injury related to blunt trauma as compared to a person with normal

coronary arteries when one considers that diseased and brittle vessels lying on the surface of the heart may be subjected to direct damage. Levy¹ believed this to be the case with the 49 year old woman in whom he observed hemorrhage within the plaque and seepage of blood through the intimal lining with thrombus formation. Moritz³ stated in his review that plaques in atherosclerotic coronary arteries are often richly vascularized with newly formed thin walled capillaries that are inadequately supported by the surrounding liquid debris and suggested that such vascular plaques are subject to spontaneous or traumatically induced rupture into the lumen of the diseased artery.

DR VLAY In a 20 year old woman however one would suspect that there is less likelihood of preexisting coronary disease. Thrombus has been suspect in the pathogenesis of traumatic coronary artery occlusion. Seven of the nine autopsied cases described thrombotic occlusion of the coronary vessel. One may speculate that shear forces during the traumatic episode may produce a small intimal tear which subsequently acquires platelets, fibrin and other clotting system components until thrombosis is complete. Spasm with subsequent thrombus formation also may occur in response to local injury although documentation of this is not available. Such a mechanism was proposed after blunt trauma to the chest of laboratory animals³ it was felt that localized blows transmitted to the precordium induced coronary spasm. Gertz¹² has presented preliminary evidence that spasm results in endothelial damage using a feline model. Spasm produced in the basilar as well as in the coronary arteries resulted in local damage and subsequent thrombosis.

DR BLUMENTHAL The findings in some patients with myocardial infarction after trauma but with normal coronary arteries on angiography¹ has raised the question of whether the injury was ever to the coronary vessel but was rather a severe myocardial contusion. Myocardial contusion has been easily produced experimentally¹³ and is frequently identified by ECG, elevated CK and other cardiac enzymes, or demonstrated by extraction or lack of uptake by a variety of radionuclide tracers.^{14,15} Nevertheless the identification of normal coronary arteries at angiography weeks to months after the infarct

| Angiogram | Autopsy | Athero- sclerotic coronary artery disease | Between trauma & symptoms of MI |
|--|--|--|--|
| | Thrombotic occlusion of LAD with large infarct | Yes (extensive) | 9 days |
| | Organized thrombus LCA recanalized Death due to RCA occlusion ten months after original infarct | Yes (extensive) | 1 hour |
| | Occlusion by thrombus 1 cm from origin | Yes (light) | Immediate |
| | Traumatic dissecting aneurysm of LAD | Yes (in significant) | 11 days |
| | Anteroseptal MI occlusion LAD by thrombus | Yes (extensive) | Immediate |
| | Occlusion of LAD at point of narrowing with hemorrhage into wall and small red fibrous thrombus blocking lumen | Yes (extensive) | 2 hours |
| | Large organizing thrombus in left circumflex | Yes (insignificant) | Immediate |
| Normal coronary arteries | | No | 10 hours |
| | Complete rupture of RCA 1 cm from orifice orifice covered with a small fresh thrombus | Yes (slight) | Immediate |
| Total obstruction in proximal LAD | | No | Immediate |
| Complete occlusion left circumflex | | No | 1 hour |
| Normal coronary arteries | | No | Immediate |
| Total occlusion LAD 1 cm from origin | | No | Immediate |
| Severely obstructed RCA 1 cm beyond its origin | | No | Immediate |
| Total occlusion RCA 1 cm beyond its origin | | No | Immediate |
| Total obstruction in proximal LAD | Proximal LAD obstructed by fibrous plaque with recanalization | No | 5 days |

did observe nine cases of complete rupture of a major coronary artery and a tenth involving an intimal tear. Sporadic reports of myocardial infarction following blunt trauma and substantiated by autopsy or angiography have appeared in the medical literature over the past 40 years.

Myocardial infarction after blunt chest trauma however as may have occurred in this young woman is rare. We could identify only 15 prior reported cases with documentation by autopsy or angiogram, and findings in these patients are summarized in Table I. Approximately 25 other reports suggesting myocardial infarction follow-

ing nonpenetrating chest injury were excluded from this review due to lack of angiographic or autopsy documentation.^{11,2} The 16 patients summarized in Table I included 13 men and three women with a mean age of 38 years (range 10 to 62 years). Eight of the 16 had atherosclerotic coronary artery disease which was described as extensive in four of them. The anterior descending branch of the left coronary artery (LAD) was involved in ten cases, the left circumflex was involved in two cases, and the right coronary was involved in four cases.

The presently described case most closely par-

transmural anteroapical and apical transmural myocardial infarct. Her coronary arteries had normal takeoff from the aorta and showed no evidence of dissection or aneurysm formation. Her proximal left anterior descending coronary artery was totally occluded by a fibrous plaque compatible with atherosclerosis or with a previous thromboembolic event with subsequent organization (Fig 4). The remainder of her coronary arteries and her aorta were completely free of atherosclerotic plaque. There was no evidence of recent infarction or coronary thrombosis to account for the terminal event.

DR BLUMENTHAL: Dr Bulkley, how do you account for the delayed presentation of the infarction?

DR BULKLEY: Most unclear and atypical in this young patient is the occurrence of the infarct five days after the blunt trauma. Of the previously reported 15 cases, only two others had evidence of delayed myocardial injury after the chest trauma, one 8 and one 9 days after the traumatic event. The ECGs and the pattern of serum creatine kinase elevation in our present patient support the clinical history suggesting that the infarct occurred five days after the trauma. Initially, the electrocardiogram revealed an acute infarct with ST-T changes that evolved with loss of R waves in the precordium. Although the precise etiology remains unknown, the precipitating event in this patient was assumed to be a coronary thrombosis and/or embolism. Unfortunately, morphologic findings five months after the event do not entirely resolve the question of etiology. An organized thrombus or embolus may be indistinguishable from a fibrous atherosclerotic plaque of long standing duration. Considering the patient's youth and absence of symptoms prior to the event, it seems likely, however, that the high grade narrowing of her coronary artery by fibrous plaque seen at autopsy in the setting for otherwise normal coronary arteries may well have been related to a thrombotic occlusion. Thus, the histologic changes in her coronary artery are compatible with, although not diagnostic of, a prior thrombotic event. The autopsy findings do provide evidence, however, that there was a coronary event related to the infarct and that the event was not a primary coronary dissection, contusion, or laceration. Furthermore, the autopsy findings show that the infarct was only in

the left anterior descending coronary artery, but not the vessel most often involved by blunt chest trauma?

DR VLAY: In ten of the 16 cases reported (63%), the vessel involved after blunt chest trauma causing myocardial infarction was the anterior descending branch of the left coronary artery. The anatomical location of this artery very likely makes it particularly susceptible to the effects of trauma. Noteworthy, however, is the predominance of involvement of this artery in cases of coronary artery embolization and dissection. Explanations advanced for the predilection of the left coronary artery in these latter conditions of embolism have included (1) the larger caliber of the left coronary artery compared to the right and (2) the geometry of the left coronary artery branches making the left anterior descending branch more liable to occlusion. Arguments against a left predominance include the fact that (1) a right coronary embolus may not be fatal or may go unrecognized and that (2) right occlusion may be more distal with less loss of myocardial tissue. With coronary artery dissection, the left anterior descending coronary artery is again the most frequently involved, usually within two centimeters of the aortic ostium, but the reason for this predominance is unclear.

DR BULKLEY: Only certain types of trauma seem to lead to this unfortunate myocardial injury. Not surprisingly, automobile accidents were implicated in eight of 16 (50%) reported cases, and many of the anecdotal accounts involve steering wheel trauma. Such injuries might be prevented by wearing shoulder harnesses and seat belts. Assault with a fist was responsible for the other three (19%) cases. The other 31% were accounted for by sporting activities and industrial accidents. In our patient, steering wheel injury, albeit mild, appeared to be the culprit. The findings in this patient and in several others reported suggest that traumatic coronary artery disease should at least be entertained in the patient with a recent persistent chest pain after chest trauma, even of a mild degree of severity. Although at the present time there is little evidence that early intervention might alter the course of this event, the recognition of an impending coronary occlusion in at least the few patients with delayed myocardial injury may offer the potential for reparative intervention.

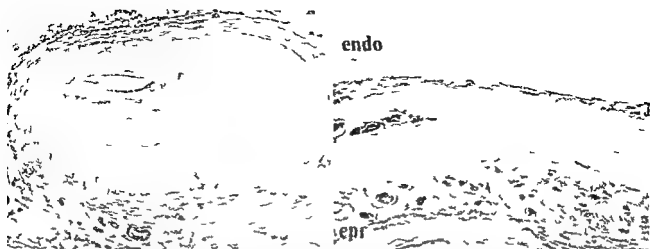


Fig 4 Left Histologic section from the proximal left coronary artery showing a near total occlusion by a fibrous plaque (Hematoxylin and eo in original magnification $\times 30$) Right Histologic section through site of anterior wall infarction showing a transmural scar a thickened endocardium (*endo*) overlying the infarct and organized epicardial (*epi*) adhesions compatible with a focal pericarditis. (Hematoxylin and eo in original magnification $\times 30$)

not sufficient to rule out acute thrombotic events as precipitating the acute infarct. Also severe coronary spasm as the result of the trauma might result in infarction but would show normal coronaries angiographically; although spasm is often noted at a site of coronary narrowing. Coronary artery embolus similarly cannot be excluded. The findings in our patient are clearly a coronary event associated with an infarct in the normal vascular distribution rather than the result of a contusion. Another unusual cause of traumatic myocardial infarction also unlikely in our patient is a frank rupture of a coronary artery.¹¹ In one patient in which it was reported¹² an acute infarct resulted from a complete rupture of the right coronary artery associated with laceration of the pericardium and herniation of the heart the latter preventing pericardial tamponade and allowing brief survival.

DR VLAY: Dissection of a coronary artery may also result from trauma,¹³ however dissection was identified in only one of the 16 patients reported. One might suggest that a small intimal tear gradually expanded over the course of six days and then suddenly proceeded to dissection. It is generally believed however that coronary dissections have a rapidly fatal course and among patients dying of coronary dissection reported in the literature¹⁴ trauma was an infrequently

associated event. A final mechanism that must be considered is coronary embolus secondary to mural thrombosis from an injured left ventricular myocardium. Levy cites Randerrath's case of the 34 year old soccer player who was struck in the chest by a ball and collapsed with pallor and cold diaphoresis with death on the following day. The autopsy revealed a recent small apical aneurysm with fresh mural thrombosis. An embolus was identified in both the LAD and the RCA.

In summary we have a 25 year old woman with flush occlusion of the anterior descending branch of the left coronary artery and infarction in its distribution who subsequently had a sudden death. Due to the absence of other angiographic lesions in her coronary tree the most likely etiology is thrombosis related to an injury to the artery or an embolic event. The cause of death most probably was a ventricular arrhythmia although infarction must not be excluded. Dr Bulkley will now present the pathologic findings.

Discussion of pathologic findings

DR BULKLEY: At autopsy the only abnormalities were present in the patient's heart and lungs. Her lungs were heavy and showed evidence of diffuse pulmonary congestion and focal areas of interlobular edema. Her heart weighed 350 grams and had left ventricular dilatation and a large

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mal or absent and there is instead a predominant systolic dip (X descent) ³

Paradoxical pulse is present as a rule in cardiac tamponade. The principal exceptions are those instances in which it may be obscured by arrhythmia or by other complicating features. In constrictive pericarditis on the other hand paradoxical pulse is usually of lesser degree than in tamponade and may be absent.

Kussmaul's sign occurs in some patients with constrictive pericarditis although probably not the majority. In cardiac tamponade however if strictly defined Kussmaul's sign occurs rarely at most perhaps never. Reported instances of Kussmaul's sign in tamponade are numerous but none are substantiated by direct pressure records; such reports probably result from failure to recognize associated constrictive pericarditis in some instances while in others an inspiratory increase in amplitude of venous pulsation may be mistaken for a true rise in central venous pressure. Still other cases represent instances where the sign is elicited with an instructed deep inspiration to which the patient responds by performing Valsalva's maneuver. The differences in special features are perhaps not so widely appreciated as they might be and the principal reason for this may be that there has been no readily understandable or generally accepted explanation for them. Indeed the mechanisms of the special hemodynamic features themselves especially paradoxical pulse and Kussmaul's sign have not been adequately understood. An additional difficulty is that clinical assessment is not so accurate or quantitative as direct pressure records in assessing these signs. Further the classification of patients is often difficult because the objective diagnosis of either cardiac tamponade or constrictive pericarditis requires a combination of clinical, hemodynamic and anatomic pathological data which are often not available in the clinical setting.

Objective diagnosis of tamponade and constriction

The objective diagnosis of cardiac tamponade defined as a condition in which there is compression of the heart by fluid in the pericardial space under increased pressure requires the measurement of an elevated level of intrapericardial pressure and of correspondingly elevated levels of pressure within the chambers of the heart in diastole. A further requirement is the return of

hemodynamic measurements to normal after removal of enough pericardial fluid to reduce the intrapericardial pressure to normal. Constrictive pericarditis is best defined as a condition in which there is compression or restriction of the heart by the pericardium either by the visceral layer or by an adherent parietal layer with hemodynamic abnormalities including elevated levels of diastolic pressure in the cardiac chambers which return to normal after surgical removal of the pericardium.

It is often difficult to meet these diagnostic criteria in clinical practice. Patients who are suspected of having cardiac tamponade because of the presence of pericardial effusion and elevated levels of venous pressure may be shown by hemodynamic study to have instead one of several other conditions alone or in combination. Some have right sided congestive heart failure due to valvular or myocardial disease with increased amounts of pericardial fluid which is not under increased pressure and represents simply one site of accumulation of excess extracellular fluid. Others especially patients on chronic dialysis for renal failure have predominantly fluid overload and left ventricular failure with an associated pericarditis and pericardial effusion of lesser importance. A few usually on the basis of neoplastic disease have superior vena caval obstruction rather than tamponade. Finally some patients have a combination of tamponade and constriction due to pericardial fluid under increased pressure associated with constriction of the heart by the visceral pericardium (epicardium); this condition (effusive constrictive pericarditis) can only be demonstrated objectively by showing that the venous pressure level remains elevated with other features consistent with constriction after the intrapericardial pressure is reduced to normal by removal of fluid ⁴

Observations in subacute constrictive pericarditis

Patients with effusive constrictive pericarditis usually have a subacute course measured in weeks or months rather than the period of years which is frequently seen in chronic constrictive pericarditis. Hemodynamic studies in these patients have provided insight into the basic differing patterns of special hemodynamic features of tamponade and constriction. In general they have features similar to those of tamponade

On the elastic and rigid forms of constrictive pericarditis*

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The effects of pericardial disease on the circulation result essentially from compression (restriction) of the heart making it more difficult for the heart to fill with blood during diastole. The function of the heart during systole does not appear to be impaired in most cases. The cardiovascular system typically achieves a compensation for compressive pericardial disease by increasing the central venous pressure to a level at which adequate filling of the heart in diastole can still occur despite the degree of restriction which the pericardial disease imposes. Thus, except in the most severe or the most rapidly developing cases where compensation is inadequate or in cases in which there are additional abnormalities of fluid balance or in the function of the heart or circulation, the clinical and hemodynamic picture of compressive pericardial disease reflects essentially a sustained elevation of central venous pressure. In this respect the two classical pericardial disorders, cardiac tamponade (compression of the heart by pericardial fluid under increased pressure) and constrictive pericarditis (restriction of the heart by a thickened and adherent pericardium) are identical.

Special hemodynamic features of pericardial disease

In compressive pericardial disease there are in addition to the elevated level of venous pressure four principal hemodynamic features which, although not unique to pericardial disease, are

somewhat distinctive and are helpful in the clinical differentiation of pericardial disease from other disorders which may also cause elevated levels of venous pressure. These features are: (1) the occurrence of nearly equal levels of pressure in all chambers of the heart during diastole; (2) the pattern of an early diastolic dip and later diastolic plateau in the ventricular pressure waveform and the corresponding prominent early diastolic dip in the atrial pressure waveform; (3) the exaggerated variation in systemic arterial pressure with respiration (paradoxical pulse) and (4) the rise in venous pressure with inspiration (Kussmaul's sign).

Equilibration of intracardiac pressure levels in all cardiac chambers in diastole is a feature common to cardiac tamponade and constrictive pericarditis, since both forms of pericardial disease typically produce compression which is symmetrical around the entire heart. However, the dip plateau waveform, the paradoxical pulse and Kussmaul's sign are known to occur in somewhat different patterns in cardiac tamponade than in constrictive pericarditis.

Hemodynamic differences between tamponade and constriction

The dip plateau pattern in the ventricular pressure waveform is a typical feature in constrictive pericarditis. In cardiac tamponade, on the other hand, there is little or no early diastolic dip; pressure in the ventricle falls only partially during the early relaxation phase of the cardiac cycle and the plateau of elevated diastolic pressure is present from the beginning of diastole. Correspondingly, the prominent early diastolic dip (Y descent) is a feature of the venous pressure waveform in constrictive pericarditis but not in cardiac tamponade, where the Y descent is mini-

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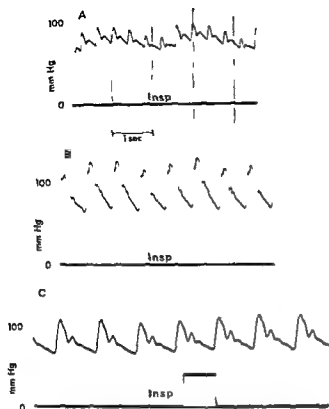


Fig 2 Varying degrees of paradoxical pulse are seen in direct pressure recordings from the aorta in patients with three types of compressive pericardial disease. The three patients are the same as those illustrated in Fig 1. At the top (A) in cardiac tamponade respiratory variation in arterial pressure is exaggerated a typical paradoxical pulse. In the middle (B) in subacute constrictive pericarditis the respiratory variation is less, but still slightly exaggerated for quiet respiration. At the bottom (C) in chronic calcific constrictive pericarditis only an unobstructed deep inspiration is followed by an appreciable fall in pressure; none could be appreciated during quiet unobstructed breathing. The unobstructed deep inspiration is indicated by Insp.

cle which is analogous to a rigid shell surrounding the heart. At the beginning of diastole when the heart is least full it is comfortably smaller than the volume of the shell and is not constricted. Thus, as the ventricular myocardium relaxes the pressure in the ventricle falls rapidly to a minimum level near zero. The combination of the high venous pressure and the unrestricted heart results in a rapid rate of blood flow into the ventricle in early diastole. As the ventricle enlarges it reaches the fixed volume of the shell and from this time through the remainder of diastole the heart is severely restricted. Any further filling during the restricted phase of diastole would be accompanied by a steep rise in pressure in the ventricle. In such cases virtually

all of the filling takes place in early diastole; restriction comes into play abruptly and the plateau of the pressure recording represents a phase in which little or no further filling takes place.

In cardiac tamponade the heart is compressed throughout the cardiac cycle. This may be inferred from the pressure recording in the pericardial space which shows an elevated pressure level throughout the cycle. The smaller size of the heart in systole does result in some decompression, but the degree of compression is more constant and less dependent on the size of the heart than it is with the rigid shell type of constriction. With tamponade, therefore, the heart is compressed from the beginning of diastole. The pressure in the ventricle does not fall to a normal level near zero, in early diastole but falls only to a level slightly above the pressure level in the pericardial fluid. Filling of the ventricle is impeded in early diastole nearly as much as in later diastole; flow into the ventricle takes place throughout diastole and the pressure waveform shows no early diastolic dip.

The lesser prominence of the dip plateau waveform in patients with effusive constrictive pericarditis can be explained as the result of a degree of associated tamponade in such cases. Its similar lack of prominence in some patients with subacute constrictive pericarditis, even in the absence of an element of tamponade or of any pericardial effusion at all suggests another explanation. Rather than a rigid shell with a fixed volume the patients with subacute constrictive pericarditis may be considered to have a fibroelastic type of constriction analogous to elastic rubber band wrapped around the heart. Such an elastic constriction would compress the heart continuously throughout the cardiac cycle in the same manner as a tense pericardial effusion. Thus the pattern of impedance to filling and the ventricular pressure waveform in subacute fibroelastic constrictive pericarditis with or without effusion might be expected to resemble that of cardiac tamponade as much or more than it would resemble that of a chronic rigid shell type of constrictive pericarditis.

Mechanism and significance of the venous pressure waveform

The diastolic portion of the central venous pressure waveform reflects directly the pressure

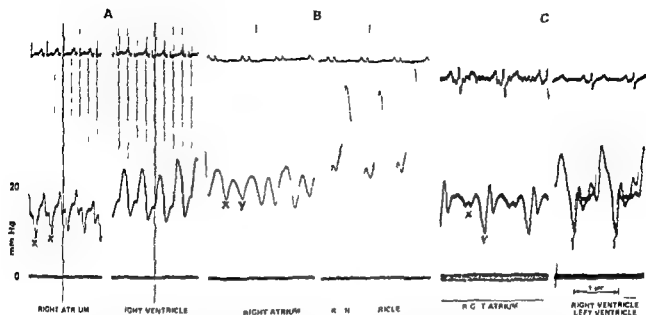


Fig 1 Contrasting waveforms are seen in pressure recordings from the right atrium and right ventricle in patients with three types of compressive pericardial disease. On the left (A) in a 17 year old woman with cardiac tamponade due to leukemia the ventricular waveform has a prominent early and late diastolic pressure level and an inconspicuous dip plateau pattern while the atrial waveform shows a prominent systolic (Y) descent and absence of the early diastolic (V) descent. In the middle (B) in a patient with idiopathic subacute constrictive pericarditis without effusion the ventricular pressure waveform shows a prominent dip plateau pattern the atrial pressure waveform shows approximately equal X and Y descents in the M or W contour. On the right (C) in a 49 year old man with idiopathic chronic constrictive pericarditis the ventricular pressure waveform shows a predominant early diastolic descent (xY pattern). All records are at the same paper speed and sensitivity.

de even though their disease process and its management is essentially that of constriction. The dip plateau in the ventricular pressure waveform is present but the dip is not so deep not approaching the zero level as it is in classical chronic constrictive pericarditis. The venous pressure waveform usually shows a predominant systolic dip with a lesser but still present early diastolic dip (xY) or a form with approximately equally prominent systolic and diastolic descents (YY). After removal of the fluid when only the constrictive element remains the early diastolic dip becomes more prominent in both the ventricular and the atrial pressure waveforms.

Paradoxical pulse is consistently present in effusive constrictive pericarditis resembling cardiac tamponade in this respect. It is relatively little affected by removal of the fluid. Kussmaul's sign may occur in effusive-constrictive cases but is probably less frequent than in chronic constrictive disease. Patients with subacute noncalcific constrictive pericarditis even in the absence of effusion also tend to show patterns of the special

hemodynamic features which are intermediate between those of tamponade and classical constriction. In this regard Wood contrasted active and inactive cases of tuberculous pericarditis while Kesteloot and Deneffe emphasized the special features of subacute constrictive epicarditis.

Thus the differing hemodynamic features in acute cardiac tamponade and chronic constrictive pericarditis represent the two extremes of a spectrum of cases. In the middle are patients with subacute constriction often associated with various degrees of pericardial effusion who show intermediate patterns of the special hemodynamic features. Figs 1 and 2 illustrate the spectrum of atrial and ventricular pressure waveforms and of the paradoxical pulse.

Mechanism and significance of the dip plateau waveform

The dip plateau waveform of the ventricular pressure recording in constrictive pericarditis is best understood as resulting from a type of mechanical impedance to the filling of the ventri-

Table 1 Comparison of the frequency and relative prominence of several clinical and hemodynamic features in three types of compressive pericardial disease

| | <i>Tamponade</i> | <i>Subacute (fibroelastic) constriction</i> | <i>Chronic (rigid shell) constriction</i> |
|---|------------------|---|---|
| Pericardial effusion | present | often present | absent |
| Pericardial calcification | absent | usually absent | often present |
| Abnormal P waves or atrial fibrillation | absent | usually absent | often present |
| Dip-plateau pattern | inconspicuous | moderately prominent | prominent |
| Venous waveform | X or Yx | Xy or XY | XY or xY |
| Paradoxical pulse | prominent | moderately prominent | inconspicuous |
| Kussmaul's sign | absent | usually absent | occasionally present |
| Early diastolic sound | absent | usually absent | often present |

The early diastolic sound of constrictive pericarditis

The early diastolic sound (pericardial knock) of constrictive pericarditis is related to the dip plateau pressure waveform in the ventricle occurring near the end of the rapid filling phase in early diastole.¹ The sound is present frequently in chronic constrictive pericarditis infrequently in subacute constrictive pericarditis and rarely if ever in cardiac tamponade. These differences are understandable in terms of the differing prominence of the dip plateau pattern in these conditions. The early diastolic sound may therefore be considered a sign of the rigid shell type of constrictive pericarditis.

Clinical implications

The clinical picture of constrictive pericarditis has changed in recent years. Tuberculosis is a less frequent cause than in the past and the chronic calcific type of disease often due to tuberculosis in the past is now less frequent than the subacute noncalcific form. The majority of cases of constrictive pericarditis today are idiopathic (including those thought to follow viral infection) while smaller numbers occur after radiation, rheumatoid arthritis, bacterial and fungal infections, chronic hemodialysis, cardiac surgery and other conditions. Constrictive pericarditis occurring in these latter conditions is in general likely to be recognized in the acute or subacute stage. Thus the features described here as being characteristic of subacute fibroelastic constriction are found in many of the patients who are seen now with an initial presentation of constrictive pericarditis.

The clinical similarity of fibroelastic constriction to cardiac tamponade and frequent asso-

ciation with pericardial effusion makes the differential diagnosis between constriction, tamponade a difficult one in many instances. The distinction is a vital one because the choice between pericardiocentesis, pericardiostomy, partial pericardiectomy or visceral pericardiectomy as well as the evaluation of the result of any of these forms of treatment depend on accurate assessment of the nature of the disease process. Measurements of intracardiac and intrapericardial pressures before and after removal of pericardial fluid are more useful than is clinical assessment in answering the questions. Study of the pressure waveforms as well as the levels of pressure is important. Table 1 summarizes the distinguishing points.

Finally the differentiation of elastic and rigid types of compressive pericardial disease may be a useful step toward understanding the mechanism of paradoxical pulse and Kussmaul's sign, conditions which have been so interesting to clinicians and physiologists for so long but which have been so difficult to answer clearly.

Summary

This article discusses a thesis regarding the pathophysiology of constrictive pericarditis. The thesis is that there are two forms of constrictive pericarditis, one being elastic and the other more analogous to a rigid shell. The two forms of constriction are considered to cause different patterns of diagnostic signs of constriction. The elastic form is similar to cardiac tamponade and is associated with prominent paradoxical pulse and a rapid descent in the venous pressure waveform. The rigid shell type has less prominent paradoxical pulse and a more conspicuous diastolic descent.

waveform in the corresponding ventricle because these chambers are in unimpeded communication in diastole. The prominent early diastolic dip in the venous pulse in constrictive pericarditis thus reflects the brief period of unimpeded blood flow into the ventricle in early diastole. Its absence in cardiac tamponade reflects the presence of compression of the heart early in diastole as well as throughout the rest of the cardiac cycle and thus the absence of a conspicuous phase of rapid filling in early diastole. Patients with subacute fibroelastic constriction are likely to show intermediate degrees of prominence of the early diastolic dip.

The systolic portion of the venous pressure waveform is influenced by several factors. There is a fall in pressure related to the descent of the ventricles due to ventricular contraction. A fall in pressure is also related to relaxation of the atria in systole following contraction of the atria just before ventricular systole. Patients with constrictive pericarditis usually show a normal systolic (X) descent if they have sinus rhythm and the venous pressure shows an XY waveform (resembling a W or M). Those with atrial fibrillation lose much of the systolic descent and usually show an XY waveform.

In cardiac tamponade there is a special circumstance owing to the phasic change in pressure in the intrapericardial space. Intrapercardial pressure falls in systole because of the degree of decompression resulting from the smaller size of the heart. Right atrial pressure falls correspondingly in systole, the two waveforms are often closely parallel throughout the cardiac cycle indicating their interdependence. Thus an X or Xv is the characteristic venous pressure waveform in tamponade.

Mechanism and significance of paradoxical pulse

Paradoxical pulse occurs by various mechanisms and in a variety of conditions other than compressive pericardial disease. The mechanism by which it occurs in pericardial disease has not been adequately understood. A variety of plausible theories have been offered and it appears that various factors may play a role. It has been accepted however since the experimental studies of Shabetai and associates supported more recently by echocardiographic studies that paradoxical pulse in cardiac tamponade is asso-

ciated with a normal or even exaggerated increase in venous return to the right side of the heart during inspiration. There is a simultaneous decrease in filling of the left side of the heart with inspiration. The increase in venous return appears indeed to be a necessary part of the mechanism of paradoxical pulse in pericardial disease.

Occurrence of the increases in volume of the right heart chambers with inspiration depends on the transmission of the inspiratory fall in intrathoracic pressure to the interior of the heart. In cardiac tamponade this transmission occurs in a normal manner probably because the pericardium is flexible and the pressure changes are well transmitted through the fluid. In constrictive pericarditis on the other hand the increase in venous return with inspiration may not occur to the normal degree because the pericardium takes the form of a rigid shell and the intrathoracic pressure variations are not transmitted to the interior of the heart. Thus the absence of paradoxical pulse in constrictive pericarditis may reflect loss of the normal inspiratory augmentation of venous return.

Patients with subacute fibroelastic constrictive pericarditis might be expected to transmit intrathoracic pressure variations to the interior of the heart more faithfully than the chronic cases who have a constrictive disease that is more analogous to a rigid shell. Paradoxical pulse would therefore be expected to be more conspicuous in the subacute cases.

Mechanism and significance of Kussmaul's sign

Kussmaul's sign may also be considered a sign of failure of transmission of intrathoracic pressure variations to the interior of the heart. The lowered intrathoracic pressure with inspiration draws more venous return to the intrathoracic venae cavae and right atrium but in the presence of the rigid shell type of pericardial disease there is no associated decrease in the compression of the heart and the increased right atrial filling is manifested as a rise in right atrial and central venous pressure. Thus Kussmaul's sign would not be expected in cardiac tamponade; it might occur in some instances of fibroelastic constriction but would be expected frequently only in the chronic rigid shell type of constrictive pericarditis.

Diet in the treatment of hyperlipidemia

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The possibility that alteration in diet may affect the risk for coronary artery disease is based on several observations. First it is generally true that the diet of those nations with higher prevalence of atherosclerotic disease differs in several respects from that consumed in nations of low risk for this group of diseases.¹ The first contains more total fat, more saturated fat, more cholesterol and total calories. Second, within populations with high prevalence for vascular disease the risk among individuals for clinical disease relates to their individual levels of plasma lipids and dietary alterations produce lowering of these levels toward apparently more favorable levels. On the basis of these facts it would seem likely that both for populations as a whole and for individual patients changes in diet from their present high fat, high calorie, high cholesterol, high saturated fat diet would be advantageous and should be expected to lessen the high rate of coronary vascular and other atherosclerotic diseases seen in American and other high risk populations. For reasons that will be discussed below, however, an unequivocal demonstration that such changes are of advantage has not been achieved and several lines of evidence raise doubts about the efficacy of such changes for the population and have made uncertain the criteria for selection of individual patients in whom such diets should be prescribed.

In contrast to the association between diet and vascular diseases seen when populations are compared to one another, the role of diet as a factor for either the level of plasma lipids or the risk for vascular disease for individuals within a given

population has not been established. With the exception of the Tarahumara Indians who have very low plasma and dietary cholesterol,² carried out in Hawaii,³ Michigan,⁴ Framingham, Massachusetts,⁵ as well as in Israel and Great Britain⁶ have failed to show a relationship between prior diet and the risk of vascular disease for individuals within this wide range of population groups. While inability to demonstrate relationship between diet and disease or value for plasma lipids may relate to problems in assessing diet histories, methodologic problems in plasma cholesterol measurement, or the fact that plasma cholesterol and/or coronary heart disease are determined by a variety of variables of which diet is only one, these studies do not provide themselves evidence that risk of coronary artery disease or cholesterol concentration within a population is determined in an important way by diet.

Similarly, studies in which diet has been altered experimentally in man to determine the effect of such alterations on the risk of coronary artery disease have been equivocal. While these and other dietary intervention studies have shown that lipids can be lowered under certain situations, it has been difficult to demonstrate that the lipid lowering has an effect on mortality. In studies carried out in Los Angeles,⁷ Norway,⁸ involving approximately 1,000 men followed for eight and 11 years, plasma cholesterol was lowered in the group given a low fat, low cholesterol, high polyunsaturated fat diet by about 15% compared to controls and there was an apparent decrease in the numbers of coronary events. Yet in neither study at a time was mortality lower in the diet group compared to the controls. Thus, lack of effect on mortality is similar to the findings in several studies in which plasma lipids were lowered by drugs.

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the venous pressure waveform often associated with an early diastolic sound (pericardial knock). Recognition of these two types of constriction may be helpful in clinical diagnosis and in understanding the pathophysiology of pericardial disease.

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is not clear however whether a subset of the population either with normal or high plasma levels is more sensitive to cholesterol intake. The major source of cholesterol in our diets is eggs and each egg contains about 200 mg of cholesterol thus a diet restricted in cholesterol below 300 mg a day greatly limits the number of eggs that can be consumed.

The amount and nature of the dietary fat also affects plasma cholesterol levels. It is well established that the cholesterol level (LDL cholesterol) is higher during the ingestion of fats comprised of saturated fatty acids than during the ingestion of polyunsaturated fats. Fats such as olive oil made up of monounsaturated fats have little effect on cholesterol levels. In general saturated fats are of animal origin such as those present in beef and pork meats and in dairy products that contain fats such as butter and cream. Polyunsaturated fats are found in vegetable oils such as corn and safflower oils and in general the fats found in fish and fowl are more polyunsaturated than those of pork or beef. While it is also generally true that foods rich in saturated fats contain more cholesterol, saturation has an effect on cholesterol level independent of that due to cholesterol intake. In most instances the cholesterol elevating effects of diet reflect the combination of an intake high in cholesterol as well as in saturated fat. The sum of these effects is a variation of plasma cholesterol of 8% to 15%. A decrease in total intake regardless of its composition that leads to weight loss produces an additional beneficial effect.

HDL or high density lipoproteins. HDL or alpha lipoproteins consist primarily of cholesterol and phospholipid and are composed of 50% protein. In normal persons the HDL cholesterol is about one third of the total serum cholesterol and averages 30 mg/deciliter in women and 45 mg/deciliter in men. Considerable evidence now indicates that in contrast to LDL the level of HDL relates in an inverse way to the risk of coronary artery disease. Except for a well established increase in HDL with weight reduction the effect of diet on this type of lipoprotein remains uncertain. Several reports suggest that increased intake of polyunsaturated fats lower HDL cholesterol. It is HDL cholesterol and a recent report on investigation also found a positive relation between cholesterol intake and HDL level. These findings require

further confirmation and the magnitude of the potentially negative effects of diet if any is yet to be established.

General considerations in the diet therapy of hyperlipidemia

1 Management aimed at altering elevated lipid concentrations should be a part of a general program for reduction of risk factors for cardiovascular disease. The two elements of this program for which evidence is most secure are the cessation or decrease in cigarette smoking and the recognition and management of hypertension. Several studies indicate that exercise will also decrease the risk for cardiovascular events. The use of diet or drugs to alter plasma lipids to decrease the risk of vascular disease is a reasonable component of therapy in patients with special risk due to elevation in plasma lipids but the efficacy of such therapy is less well established than that for the other modalities discussed above.

2 Studies of the effect of diet on mortality have been disappointing but have been largely limited to patients with or without heart disease who are beyond the middle age. These findings and the pathological evidence concerning the time course of atherosclerotic disease suggest that if diet is of value in prevention of this disease it will have to be instituted early in life. There is no real basis for the institution of diet therapy of abnormal plasma lipids or in general for the prevention of atherosclerosis in patients older than 65 years.

3 Diet therapy should generally be determined by the nature of the pattern of abnormality in plasma lipid concentration. In evaluating a patient with hyperlipidemia total plasma cholesterol, plasma triglyceride and HDL cholesterol should each be measured. These values should be obtained in patients who are following the normal patterns of activity and food intake or who have not recently suffered a serious illness such as a myocardial infarction. Although the cholesterol values are not altered immediately by meals triglycerides are therefore plasma lipids should be determined at least 10 hours after the last ingestion of fat.

Although our understanding of hyperlipidemia is based on the concept of transport of lipids as lipoproteins, lipoprotein electrophoresis is helpful in evaluation and treatment.

Dietary factors and lipoproteins

It is now clear that an understanding of the relationship between plasma lipids the risk of vascular disease and attempts to alter this risk of diet requires consideration of these lipids as components of circulating lipoproteins. There are four lipoproteins that occur in the plasma of normal persons and elevations in their levels reflects in almost all instances an increase in these lipoproteins rather than the presence of abnormal forms. These lipoproteins are affected differently by dietary manipulations and have different statistical relationships to the risk for vascular disease. In most instances with the exception of high density lipoproteins (HDL) measurement of cholesterol and triglyceride will suffice and the lipoprotein pattern can be predicted from these values making direct measurement of lipoproteins unnecessary.

Chylomicrons Chylomicrons are lipoproteins made up almost entirely of triglyceride and they relate directly to fat ingestion in that they are produced by the intestine during fat absorption and do not appear normally in plasma except during the six to ten hours following fat intake. Increase in plasma chylomicrons in the fasting state are not an important component of hyperlipidemias in man and in rare instances in which their concentration is increased they seem to have a weak association if any with increased risk for vascular disease. For that reason they will not be discussed further except to make the general statement that they are reduced in plasma when fat intake is curtailed.

VLDL or pre beta lipoproteins The lipoprotein other than chylomicrons that are rich in triglyceride is the VLDL or pre beta lipoprotein. This lipoprotein is present at elevated levels in almost all adult patients with hypertriglyceridemia. The amount of this lipoprotein in plasma has a direct relation to the risk of vascular disease. It is increased in many patients with obesity particularly with high insulin concentrations and it is also seen at elevated levels in many diabetic patients of the insulin independent or maturity onset type. It has repeatedly been shown that weight reduction regardless of the composition of the diet results in most subjects in a decrease in plasma triglyceride (as VLDL) as well as in the accompanying hyperinsulinemia. The long term effects of weight reduction with or without accompanying fall in plasma triglyceride upon

the risk of developing cardiovascular disease remains uncertain.

In the patient with hypertriglyceridemia (elevated VLDL) who is not obese or in the patient who has achieved maximal weight loss but who remains hypertriglyceridemic the effect of diet is considerably less certain. When normal persons or patients with hypertriglyceridemia are given a diet restricted in fat with a high carbohydrate content elevation in triglyceride occurs at least transiently. Many authors believe that this response is temporary and that this diet coupled with cholesterol restriction and restriction of saturated fat is optimal therapy in patients with elevation of plasma triglyceride and in whom weight loss has been unsuccessful. Other authors however have found that fat restricted high carbohydrate diets with total caloric content sufficient to maintain weight lead to increase in triglyceride concentration particularly postprandially. In practice however this problem is rarely encountered since diet modified to restrict fat usually results in a decrease in total triglyceride which in itself has a favorable effect on triglyceride concentration.

LDL or low density lipoproteins This lipoprotein contains mainly of cholesterol and most plasma cholesterol circulates in this form. The well established direct association between plasma cholesterol concentration and the risk of vascular disease reflects variations in this lipoprotein. Most of the variation in the plasma cholesterol within the normal population results from variations in the amount of this lipoprotein and in almost all instances elevations of cholesterol to abnormal levels in the absence of hypertriglyceridemia reflect increased levels of beta lipoprotein.

It is now clear that in man alterations in cholesterol intake without other changes in diet affect its plasma level. There is however uncertainty about the magnitude of this effect and the level of cholesterol intake beyond which such an effect can no longer be seen. The average intake of cholesterol in the United States is 500 to 600 mg per day and it seems likely that increases beyond that range may have a small impact if any on the plasma level. In fact the major effect of dietary cholesterol seems to be demonstrable only when cholesterol intake is in the range of 300 mg per day and below and at that range restrictions in intake seem to produce decreases in plasma levels of about 10% to 15%. It

The importance of the history in the medical clinic and the cost of unnecessary tests

The use of routine investigations in the medical outpatient department is widespread. The experienced doctor however realizes the limited value of such investigations and the importance of the clinical history and less so of the clinical examination in the diagnosis and management of patients. To try to measure the usefulness of the three basic clinical methods—history examination and investigation—a two year study of medical outpatients was undertaken in a typical district general hospital serving a largely urban population of 225 000 people.

All new patients referred by a family physician to a general medical clinic with a cardiological bias were included in the study. The new patient was examined at his first attendance by the medical registrar or senior house officer who took a detailed history. Routine investigations in all patients comprised hemoglobin, white cell count, erythrocyte sedimentation rate, blood urea, serum electrolytes and blood sugar estimations, chest radiograph and electrocardiogram. In addition any appropriate special investigations were also arranged such as exercise tests, barium studies, electroencephalography etc. After a short interval the patient returned to the clinic to see me when the following steps were undertaken:

- 1 The referral letter was read carefully and a note was made on whether a specific diagnosis was offered or whether referral was on the basis of symptoms/signs only.
- 2 The history obtained at the first attendance was read and supplemented by any relevant questions that had been omitted by the junior staff.
- 3 A specific diagnosis was made where possible and the management was decided on the basis of this completed history. Management could be referral back to the family physician with or without treatment, follow up in the medical clinic again with or without treatment, hospital admission or referral to another hospital department.
- 4 The initial examination findings were studied and any omissions again were made good by me.
- 5 The diagnosis and management based on the history were reviewed in the light of the examination findings and any necessary modifications were made.
- 6 Finally the investigations were assessed and any contribution by routine investigation or special investigation to diagnosis and management was assessed.

To check the accuracy of the hospital diagnosis a questionnaire was circulated to family physicians 18 to 30 months after the initial referral asking whether the diagnosis was still considered correct or whether any new developments had occurred to alter the hospital diagnosis. This questionnaire was not however sent in relation to all patients seen. Where the hospital diagnosis confirmed the physician's diagnosis—for instance in anginal patients—or where objective findings placed the diagnosis beyond doubt—as in hypertension, rheu-

matic heart disease, diabetes, thyrotoxicosis, etc.—no follow-up was considered necessary.

In the two year period 630 outpatients were seen. The use of the history examination and investigations in diagnosis is shown in Table I. The history decided diagnoses in two thirds of the cardiovascular and clinical examination contributed to only one-quarter of cases.

When the 180 patients with chest pain are separately considered the history gave the diagnosis in 90% and examination was of no diagnostic value at all. Routine investigations, mainly chest radiographs and electrocardiogram, helped with only 3% of diagnosis and special tests, exercise electrocardiography helped with 6%. The value of the history was also high in neurological with examination contributing even less than in the other problems and routine investigations were again of value.

The history was also the main diagnostic method in urinary and miscellaneous problems. It was of value in alimentary problems, where the main diagnostic was provided by the special radiological tests. Special investigations were also of primary diagnostic value in endocrine problems. Clinical examination and routine investigations were of no help in alimentary problems and little in urinary problems.

The importance of the history examination and investigations in deciding management is shown in Table II. The history was the major determining factor in the large neurological, respiratory and miscellaneous problems. Examination was most helpful in respiratory disease in diagnosing chronic bronchitis and emphysema, and less so in cardiovascular problems, where the main value was hypertension and rheumatic heart disease. Examination helped least in alimentary problems. Routine investigations were of least value in cardiovascular and neurological problems and of most value in endocrine problems, mainly to blood sugar concentrations in diabetic patients. Also the routine chest radiograph was important in the management of respiratory problems, and routine investigation was helpful in urinary problems. The special investigations were again of most value in alimentary and endocrine problems.

The incidence of abnormal results in all the routine investigations is shown in Table III, which also indicates whether the abnormality relates to the primary condition for which the patient was referred or to an associated unsuspected clinically significant condition. The limited number of positive results with every investigation in every group of patients was obvious. The over all incidence of positive blood or urine results did not exceed 10% and when considered in relation to the primary condition for which the patient was referred,

4 In patients with hypertriglyceridaemia with or without moderate elevations of cholesterol the most important diet therapy is weight loss. The patient should be made aware that the basis for a weight reduction program has specific therapeutic implications and that even moderate degrees of weight loss may be associated with decrease of plasma triglycerides towards normal levels even if optimal weight is not achieved.

5 In patients with hypercholesterolemia in the absence of hypertriglyceridemia the diet should include the three elements of diet known to lead to cholesterol reduction—restriction of saturated fat provision of at least 10% of calories as polyunsaturated fats as well as a decrease in cholesterol intake. In general terms this is a diet that restricts egg intake the ingestion of beef and pork products (including fat containing dairy products) and requires the addition of unsaturated fats in the form of vegetable oils and soft margarine. In addition to eggs or animal meats such as liver kidney are also very high in cholesterol content. The most favorable sources of protein are fish and fowl. In general shell fish such as lobsters and shrimp contain as much cholesterol per gram of protein as do beef and pork products. The value of total fat restriction in a cholesterol lowering diet is not fully established. Since there are marked individual variations in the response to this type of diet it is important to measure the effectiveness of the diet program after approximately four weeks of treatment. In patients with serious elevations of their cholesterol concentrations in whom such therapy is ineffective therapy with drugs should be instituted.

8 Alcohol ingestion has a complex relationship to plasma lipid and development of atherosclerosis. In general high levels of alcohol ingestion seem to be associated with increase in VLDL triglyceride particularly in persons whose levels are already elevated. There is little if any effect on LDL, but an increase in HDL cholesterol has been shown. Thus alcohol could be advantageous or disadvantageous although most studies show that when ingested at more than moderate rates alcohol is associated with increases in mortality rates. The relationships between alcohol and coronary heart disease and its individual risk factors are discussed in a recent review.

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Table IV Cost of routine investigations in patients already diagnosed on basis of history and examination

| | Total no of patients | No of patients diagnosed | Cost of routine investigations in diagnosed patients (£) |
|----------------------------------|----------------------|--------------------------|--|
| Cardiovascular | 276 | 257 | 3 107.38 |
| Neurological | 119 | 89 | 1 101.82 |
| Endocrine | 60 | 31 | 383.78 |
| Alimentary | 52 | 14 | 173.32 |
| Respiratory | 36 | 25 | 309.50 |
| Urinary | 19 | 12 | 148.56 |
| Miscellaneous | 63 | 34 | 420.92 |
| Total cost in the two year study | | | £ 5 645.28 |
| Cost per year | | | £ 2 822.64 |

In the follow up questionnaire to the family physician on the original hospital diagnosis in 548 patients there was a 60% response and the overwhelming majority of the answers confirmed the original diagnosis.

The cost of the routine investigations in those patients already diagnosed on the basis of the history and the examination is shown in Table IV. The annual cost in the Medical Clinic was £2,823 (approx \$6,500 U.S.). A small survey among 28 physicians in the Trent Region to discover how many carried out routine investigations in their new outpatients similar to the procedure in the present study showed that 43% did so. If this pattern was reflected nationally among the 1 044 hospital physicians employed in the N.H.S. the total annual cost to the N.H.S. of these useless investigations would be £ 1 266 083 (almost 3 million dollars U.S.).

The study has clearly shown the major importance of the history in deciding the diagnosis and management of 630 medical outpatients. These findings support the views expressed by Platt on the vital importance of the history in clinical medicine. Similar findings were also reported by Hampton and associates in a more limited study of 120 medical outpatients. Clinical examination contributed much less diagnostic help its main benefits being confined to cardiovascular problems in the detection of hypertension and valvular heart disease and in respiratory problems in indicating chronic bronchitis and emphysema. Similar results emerged in relation to the major value of the history in patient management with much less help provided by examination findings.

Routine blood count, erythrocyte sedimentation rate, blood urea and serum electrolyte estimations were of primary diagnostic help in only 11% of patients. Overall routine urine examination and blood sugar estimation also contributed little to diagnosis apart from 11% of patients. Chest radiographs were slightly more helpful in diagnosis of respiratory and cardiovascular problems. A further 11% of patients had abnormal electrocardiograms and blood sugar estimations in diabetes mellitus. Chest radiographs and

electrocardiograms in respiratory and cardiovascular problems are hardly "routine" since they are specifically indicated to these problems.

The special investigations were of more value in diagnosis and management. The most useful were barium meals and cholecystograms, which decided most of the alimentary diagnostic problems. Thyroid function tests and glucose tolerance tests were also of considerable help in the appropriate endocrine disorder. The exercise electrocardiogram contributed little in cardiovascular problems and the electroretinogram was also of minor value in neurological problems.

What are the implications of the present study? First and foremost is guidance on the educational requirements of medical students. Conventional training is based on a combination of history and examination findings before the diagnosis is considered. A similar system is widespread in published case presentations in medical journals. Much greater emphasis should be placed on the diagnostic and management value of the history. Students and postgraduates should be well trained in taking a good history and in drawing diagnostic conclusions from the history before embarking on the examination. This will encourage the student to seek specific examination findings to confirm or refute the diagnosis based on the history. The traditional case presentation of history and examination followed by differential diagnosis should be changed to history, differential diagnosis, and relevant examination findings. A similar approach could be encouraged in medical journals and textbooks where inadequate emphasis on the importance of the history is often all too evident.

The study has also shown clearly the limited value of routine blood investigations. Some doctors may carry out these routine investigations because they think it makes their approach more scientific; others, perhaps, because they fear they might miss some other serious coexistent condition; yet others may consider it desirable to have baseline measurements of these parameters to compare with possible future disorders. Emphasis on the scientific investigational approach, however commendable though this may appear, could lead to unselective application of laboratory investigations and minimize the importance of good history taking in diagnosis and management. The value of the routine blood and urine investigations in the present study in showing unsuspected significant coexisting disease was small, only 9.5% of patients. A similar limited incidence of unsuspected abnormal routine laboratory results was also reported by Hudd in a study of 200 medical outpatients.

Another important consideration is the cost of laboratory routine investigations. In the Barnsley District General Hospital alone an annual saving of £2,823 (\$6,500) could have been achieved in one medical clinic by omitting routine investigations in patients in whom the diagnosis had already been made on the basis of the history and clinical examination, and if the national picture followed the pattern of the local area, carried out in the Trent Region an annual total of over £12 million could have been saved.

The justification for any investigation should surely be to answer a specific clinical question relating to diagnosis and management only when there is doubt as to either or to measure the effect of treatment that cannot be assessed on symptoms or signs alone. Where these requirements are not operative however and where the result of the investigation

Table I Diagnostic value of history examination and in 1971

| Referral diagnosis | No of patients | History | Examination | Total | |
|--------------------|----------------|---------|-------------|----------|----------|
| | | | | Positive | Specific |
| Cardiovascular | 276 | 87 | 33 | — | — |
| Neurological | 119 | 6 | 17 | — | 14 |
| Endocrine | 63 | 22 | 1 | 11 | 42 |
| Alimentary | 53 | 3 | — | — | — |
| Respiratory | 36 | 4 | — | 1 | 18 |
| Urinary | 19 | — | 1 | — | — |
| Miscellaneous | 63 | 4 | — | — | — |
| Totals | 630 | — | — | — | 1 |

Table II Management value of history examination and in 1971

| Referral diagnosis | No of patients | History | Examination | Total | |
|--------------------|----------------|---------|-------------|----------|----------|
| | | | | Positive | Specific |
| Cardiovascular | 276 | 87 | 33 | 4 | 13 |
| Neurological | 119 | 6 | 17 | 3 | 21 |
| Endocrine | 63 | 11 | 1 | 1 | 4 |
| Alimentary | 53 | 13 | — | — | — |
| Respiratory | 36 | 4 | — | 1 | 1 |
| Urinary | 19 | — | 1 | — | — |
| Miscellaneous | 63 | 4 | — | 11 | — |
| Totals | 630 | 4 | — | — | 24 |

Table III Incidence of abnormal routine investigations in 1971

| | No done | Hb/WCC | | ESP | | ECG | | Chest radiograph | | ECG | |
|----------------|---------|--------|----|-----|---|-----|---|------------------|----|-----|---|
| | | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 |
| Cardiovascular | 276 | 1 | 0 | 2 | 1 | 0 | — | 1 | 0 | 1 | 1 |
| Neurological | 119 | 0 | 4 | 0 | 1 | 0 | — | 1 | 0 | 1 | 1 |
| Endocrine | 63 | 0 | 3 | 0 | 1 | 1 | — | 4 | 1 | 0 | — |
| Alimentary | 53 | 0 | 1 | 0 | 0 | 0 | — | 1 | 0 | 1 | 0 |
| Respiratory | 36 | 1 | 0 | 2 | 0 | 0 | — | 1 | 0 | 0 | — |
| Urinary | 19 | 0 | 1 | 1 | 0 | 1 | — | 0 | 0 | 0 | 0 |
| Miscellaneous | 63 | 4 | 1 | 1 | 0 | 0 | — | 1 | 0 | 0 | 1 |
| Totals | 630 | 6 | 19 | 6 | 3 | 1 | — | 19 | 21 | 4 | 4 |

From primary diagnosis for which patient was referred.

On period co-existence but clinically significant condition.

diagnostic help in even less. The most useful routine tests were the chest radiograph and electrocardiogram, but even they were of primary diagnostic help in only 5% and 12% respectively.

The diagnostic value of the more specific special investigations was greater. A positive test occurred most often with the radiogram in respiratory problems, but even then it decided the diagnosis in only 11%. The glucose tolerance test was of

the greatest diagnostic value of all the special tests, diagnosing 70% of the diabetic problems. Barium meal tests and cholecystography contributed substantially to the diagnosis of alimentary problems. The electroencephalogram, though often positive, decided the diagnosis in only 15% of cases. Echocardiogram and brain scan were of no value. Thy function tests were of considerable diagnostic value. Exercise test was of negligible diagnostic help in chest pain.

Table 1 Conditions where ASH is reported to occur

| Condition | No of cases/ Total cases | % of cases |
|-----------------------------------|-----------------------------|------------|
| Acromegaly | 8/9 | 88 |
| Malignant hypertension | 14/30 | 46 |
| Chronic renal failure | 7/23 | 30 |
| Systemic hypertension | 12/40 | 30 |
| Systemic hypertension | 3/30 | 10 |
| Systemic hypertension | 9/234 | 4 |
| Mitral valve prolapse | 16/190 | 8 |
| Aortic valve disease | 5/59 | 8.5 |
| Mitral valve disease | 2/36 | 5.5 |
| Aortic & mitral valve disease | 3/37 | 8.1 |
| Coronary artery disease | 4/79 | 5 |
| Miscellaneous cardiac diseases | 8/100 | 8 |
| Miscellaneous cardiac diseases | 40/100 | 40 |
| Aortic stenosis & bicuspid valves | 5 | — |
| Weight lifters | 14/14 | 100 |
| Athletes | 4/10 | 40 |
| Normal subjects | 5/10 | 50 |

In index patients with posterior infarction and congenital heart disease

show patients in whom the septum and posterior wall are of equal thickness. There are only four echocardiograms which claim to show ASH and the interpretation of some of these is questionable. While we do not deny that ASH can occasionally occur in conditions other than IHSS it is in our experience an infrequent finding. Therefore rather than report our own experience (which might be open to dispute) we reviewed the left ventricular echocardiograms published in widely available echocardiographic textbooks and in current cardiology journals. These contained numerous high quality echocardiograms from patients with those conditions listed in the table in which the thickness of the septum and posterior wall could be confidently measured. We found no examples of ASH but on the contrary in all cases the thickness of the septum and posterior left ventricular wall were found to be remarkably similar.

There are several technical problems and pitfalls in the recording of echocardiograms in the measurement of septal and posterior wall thickness. In relatively small errors can lead to significant errors in ASH. For example it is easy to confuse the echocardiographic appearance of chordae or papillary muscles with the echocardiographic appearance of the septum and posterior wall. In the case of the septum, overestimation of thickness can be caused by use of the incorrect angulation of the sector scan. In the case of the posterior wall, artefact due to the use of a sector scan with a wide beam width can lead to an overestimation of thickness. In the case of the septum, overestimation of thickness can be caused by use of the incorrect angulation of the sector scan. In the case of the posterior wall, artefact due to the use of a sector scan with a wide beam width can lead to an overestimation of thickness. In the case of the septum, overestimation of thickness can be caused by use of the incorrect angulation of the sector scan. In the case of the posterior wall, artefact due to the use of a sector scan with a wide beam width can lead to an overestimation of thickness.

In view of the technical problems involved in the measurement of septal and posterior wall thickness, it is not surprising that published echocardiographic studies have reported ASH in conditions other than IHSS.

ventricular hypertrophy the question arises as to whether some of the cases of ASH in these reports are erroneous. A sceptical reader may be justified in not accepting a significant association between ASH and the conditions listed in the table until he is able to measure for himself in such reports echocardiograms clearly demonstrating ASH. Because even in any publication is limited, composite illustrations containing echocardiograms from several patients with no more than one cardiac cycle from each could be provided.

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whether positive or negative is unlikely to change either the diagnosis or management of the patient, there can be no justification in asking for it.

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Of saphenous vein arteriosclerosis

The saphenous vein *in situ* never develops atherosclerotic changes. It can develop phlebosclerosis if there are varicose veins or an arteriovenous shunt in the area. But, if a segment of the vein is used for coronary artery bypass surgery it develops arteriosclerosis. Why there and not in the leg? It must be due to the intraluminal pressure of the venous segment when it is used for the aorta-coronary shunt and the trauma to the venous segment associated with its isolation and transplantation. The exposure to tobacco, diet, blood substances, etc., is the same and is present for all veins as well as for all arteries. As pointed out previously, intra-arterial pressure and now high intravenous pressure in the venous segment, is an important factor in the production of arteriosclerosis. Arteriosclerosis can be due in part to the anatomic and other disturbances associated with the system related to removal and transplantation of the venous segment. The areas of trauma can provide the nidus for the "arteriosclerosis" to develop. The beating heart and the chronic adhesive pericarditis associated with venous aorta-coronary bypass must produce further physical trauma to the saphenous

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vein segment as the heart moves about during each heart beat. This could be an additional factor which contributes essentially to the production of arteriosclerosis in the venous segment. A study of such a venous bypass segment could contribute to understanding the pathogenesis of arteriosclerosis.

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Asymmetric septal hypertrophy in conditions other than IHSS

Since asymmetric septal hypertrophy (ASH) was first demonstrated by echocardiography in patients with idiopathic subaortic stenosis (IHSS) and in some of their first-degree relatives, it has been reported in many other conditions. These conditions can be divided into two groups. First, there are those disorders where the interventricular septum might be expected to be thicker than the posterior left ventricular wall—i.e., inferior myocardial infarction and right ventricular hypertrophy—whether due to primary pulmonary hypertension

or to congenital heart disease. Secondly, there are a large number of conditions where the presence of ASH could not be anticipated (Table I). It is the purpose of this annotation to draw a tension to the contrast between, on the one hand, the plethora of reports of ASH in this latter group and, on the other, the paucity of published echocardiograms supporting them.

Only some of the publications listed in the table are illustrated by echocardiograms, and curious, most of these

neurons involved. The consequence will be overeating. Many obese people are compulsive eaters and their cravings for food are often uncontrollable. Their condition has been described as carbohydrate addiction. We think that the resemblances to narcotic addiction support our proposal of a common opioid mechanism. Considering the unpleasant mental symptoms during withdrawal from morphine addiction it would be surprising if there were not some psychological symptoms associated with autoaddiction.

Eating between meals

Enkephalin differs from morphine in its short half life: less than a minute, so as soon as the food leaves the duodenum there will be a rapid disappearance of enkephalin from the environs of the receptor neuron. This contrasts with the relatively slow removal of morphine from the circulation. This disappearance of enkephalin about a couple of hours after a meal will cause excessive activity in dependent neurons and will constitute a withdrawal syndrome before the next meal is due. Eating snacks between meals will abate the consequent cravings for food and of course eating between meals is a common feature in obesity.

Sugar

It is a general observation that sugar has a special relationship to appetite and to satiety. We can for example eat a sweet when we are already replete with the savoury meat and vegetable course. Sugar must have been a rare item in the diet of preagricultural man and the evolution of the satiety system must have taken place with a relatively sugar free duodenum. In the intracellular digestive assay for the estimation of caloric value the direct diffusion of sugars into the cell might well swamp the process. With an average daily consumption of about 130 g. of sugar the sweet products of modern food technology may result in many people today being unable naturally and unconsciously to regulate their food intake.

In conclusion if we are not all to be in a perpetual state of

addiction the maximum enkephalin released by the sensory cells must not regularly exceed the amount required to maintain the activity of the receptor neurons. While the system can cope with episodic excess chronic excess of enkephalin must be pathological, and even a small regular excess could have some degree of autoaddiction.

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Effect of oral disopyramide on serum digoxin levels. A prospective study

Recent published studies have shown that digoxin levels may lead to increased toxicity if serum digoxin levels are increased. Therefore we studied the effect of oral disopyramide on serum digoxin levels.

Ten patients with chronic heart failure were given a daily stable dose of digoxin 1.25 mg and a daily dose of disopyramide 150 mg.

In all patients, digoxin levels were determined on Tuesday and Friday at the same time interval after the last administration. Then oral disopyramide was given for 7 days in doses individually ranging from three to six tablets daily. Both digoxin and disopyramide levels were determined on Tuesday and Friday of the third week of the study. Comparable time intervals to the first week were used for the second week.

As shown in Table 1, prior to disopyramide administration serum digoxin levels varied from 0.8 to 2.5 nmol/l (mean 1.2 nmol/l). In the same patient the digoxin level varied from 0.4 (mean 0.1) nmol/l during disopyramide administration.

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Autoaddiction a hypothesis on hunger and obesity

During the past ten years a group of some seven peptides with putative neurotransmitter and hormonal function have been found both in the brain and the gut. One of these, enkephalin, has aroused special interest because it occupies the same receptor sites as morphine. Experiments in the brain have shown that neuronal pathways, already firmly associated with the reduction of hunger drive, are most probably part of an enkephalinergic system. Our proposal links this work with the enkephalin-containing cells in the gut to constitute a system which responds to the appropriate amount of food in the stomach by switching off eating. It gives the sensation of satiety and the feeling of postprandial well being, and keeps us from a consideration of the opioid nature of the system. We arrive at a feasible dysfunction by which a person can become addicted to his endogenous opiates, a condition which we have called "autoaddiction."

Satiety

Experimental work has shown that satiety and cessation of feeding are elicited by samples of food from the stomach activating receptors in the wall of the duodenum. We propose that enkephalin is a mediator. In the gut, enkephalin is found in the highest concentration in the antrum of the stomach and in the duodenum, both in neurons and in open-ended secretory cells. The enkephalin-containing cell is probably a receptor cell, sampling the contents of the duodenum at a local open end of the cell and releasing enkephalin as a local hormone at the other. We propose that the released enkephalin inhibits nearby afferent enkephalinergic neurons. The switch off feeding and the hunger drive in the brain. The strength of the reward depends on the number of secretory

cells recruited by the influx of food into the duodenum. The secretion of enkephalin from each can do no more than inhibit the activity of the neuron.

Addiction

All the indications are that endogenous opiates are at least as addictive as morphine, and we can see no good reason why the release of excess enkephalin should not be as addictive as circulating morphine. We assume that addiction involves cellular changes as in the theory proposed by Collier, in which opiates act by inhibiting the production of cyclic AMP and hence the activity of the neuron. Continued inhibition leads to an increase in the capacity of the neuron to make more cyclic AMP, and so it will need more opiate to suppress it (tolerance). The removal of the excess opiate unleashes the increased capacity to increase cyclic AMP and the resultant hyperactivity of the neuron is the cellular equivalent of the withdrawal syndrome.

Autoaddiction and obesity

If for example the receptor-secretory cells in the duodenum overproduce and release too much enkephalin (or if the released enkephalin is not degraded with sufficient rapidity) then the regular excess of enkephalin over and above the amount required to reduce the activity of the receptor neuron will have the same effect as circulating morphine. Repeated regularly after meals the excess enkephalin like uniform doses of morphine will soon cease to satisfy. Tolerance/dependence will develop. Some neurons cannot now be switched off by the released enkephalin and the satiety mechanism fails to an extent, depending on the number

ity may be responsible²⁴ recent reports have indicated the possible causative role of the renin angiotensin system in the generation of the increased peripheral vascular resistance

Increased levels of plasma renin and plasma renin activity have been reported during conventional CPB²⁵ Increase in the plasma level of angiotensin I has also been reported. In a previous study the author and his colleagues have demonstrated a marked rise in plasma angiotensin II (AII) levels during nonpulsatile CPB with persistence of these elevated levels for around two to four hours postoperatively. These elevated levels of plasma AII are significantly greater than those found during or after major non bypass procedures. Elevation in the plasma level of angiotensin II during and after the period of CPB might therefore be considered likely to be of significance in the development of increased levels of peripheral vascular resistance

In view of this possible association between increased plasma AII levels and increase in vascular resistance 19 consecutive patients who had submitted to elective open heart surgical procedures were studied. Six patients had prosthetic valve replacement procedures and six had coronary artery bypass grafting. The mean age of the patients was 52 years. There were seven males and five females. Conventional nonpulsatile CPB was used in all cases with a bubble oxygenator. The pump flow was calculated according to the standard formula

$$\text{Flow} = 2.4 \text{ L/m}^2 \text{ min}$$

The mean total bypass time was 92.3 minutes, the mean temperature during perfusion was 35.5 °C and the mean packed cell volume during bypass was 20%.

In each patient blood samples for plasma angiotensin II estimations were obtained on full pump flow at the onset of total CPB and on full pump flow at the end of total CPB. At these times measurements were obtained allowing the calculation of peripheral vascular resistance index. Peripheral vascular resistance index (PVRI) was calculated according to the formula

$$\text{PVRI} = \frac{\text{mean arterial blood pressure} - \text{CVP}}{\text{cardiac index}}$$

Plasma angiotensin II levels were measured by the standard radioimmunoassay method. In each of the 12 patients studied PVRI rose during CPB from a mean level of 20.87 ± 1.21 SEM to an end CPB level of 27.83 ± 1.61 SEM. The mean rise in PVRI during bypass was 6.96 index units. In percentage terms this is an increase in vascular resistance of 33.3%. Similarly plasma angiotensin II levels rose during bypass from a mean level of $18 \text{ pg/ml} \pm 1.6$ SEM to a mean end bypass level of $231 \text{ pg/ml} \pm 11.8$ SEM (normal plasma AII level = $< 35 \text{ pg/ml}$). The rise in plasma angiotensin II levels was correlated with the rise in peripheral vascular resistance index levels for each of the 12 patients. The correlation coefficient obtained (r) was 0.91. This indicates a highly significant correlation between the quantitative change in plasma angiotensin II levels and the quantitative rise in peripheral vascular resistance index ($p < 0.001$).

This study lends support to the concept that activation of the renin angiotensin system during conventional nonpulsatile CPB with the consequent elevation in the plasma level of angiotensin II may be a significant factor in the development of increased vasoconstrictor during and after open heart

surgical procedures. If this is indeed so there are important therapeutic considerations regarding the management of the vasoconstriction. It is increasingly recognized that reduction in elevated levels of vascular resistance is beneficial²⁶ to the majority of patients in the early period after open heart surgery. Several authors have recently demonstrated significant improvement in hemodynamic status in patients after open heart surgery who received vasodilator therapy. For example with nitroglycerine²⁷. This benefit was considered to reflect improvement in left ventricular performance. If angiotensin II is of major etiological significance in post-bypass vasoconstriction specific therapy designed to counteract the vasoconstrictive effect of angiotensin II would offer theoretical advantages over nonspecific vasodilator therapy, particularly in relation to the known physiological effect of angiotensin II in producing increased subendocardial ischemia. Specific anti AII therapy therefore offers a possible therapeutic superiority over current therapies (e.g. nitroglycerine) in blocking the coronary vasoconstrictor effect of angiotensin II in addition to reducing elevated vascular resistance levels.

In this regard recent reports using angiotensin converting enzyme inhibitor substance have suggested that such theoretical advantages of specific anti AII therapy may in fact be evident in clinical practice. If however we continue to hold the maxim that prevention is better than cure attention ought also to be directed towards the prevention of the excessive activation of the renin angiotensin system by modifying cardiopulmonary bypass perfusion. The use of pulsatile flow during CPB is widely reported in the literature to be associated with significantly lower levels of vascular resistance compared to conventional nonpulsatile perfusion. It may be that this hemodynamic effect of pulsatile CPB is achieved by means of reduced activation of the renin angiotensin system producing significantly lower levels of angiotensin II during the period of perfusion and in the early post bypass period.

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neat and to lie with the hauline. Cerebral blood flow and oxygen utilization increased. The first patient of the series had a striking improvement in power. Before the operation his right arm had been totally paralyzed for six weeks and within ten days of the procedure movement appeared first at the shoulder then at the elbow and finally at the wrist. At the end of six weeks his arm movements were completely normal. Three months later his inaccessibly stenosed internal carotid artery occluded and he suffered a recurrent completed stroke. His deficit on this occasion was severe but the arm was relatively spared. Most patients had a reduction in tone with improvement in power enabling an improvement in gait and stability.

Psychological assessments were performed before and after operation in seven of the nine patients. Improvement was claimed in six out of seven. The left sided bypasses produced a striking improvement in verbal tests and intellectual improvement of one sort or another was demonstrable in all but one patient.

The preliminary results suggest that extracranial to intracranial bypass may produce an improvement in some patients with longstanding moderate completed ischemic stroke. As some of the patients in the report had a long standing total paralysis of the arm before surgery these deficits may have been regarded as too severe to fall within the criteria for entry into the Canadian cooperative study.

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Of cardiac causalgia, Horner's syndrome, and the cardiac dermatome

It is worthy of note that cardiac causalgia is practically limited to the left side of the chest wall, left lung, left side of the head and neck, and left shoulder and left arm. The left shoulder is regularly involved in this syndrome (postinfarct and postcardiotomy or Dressler syndrome). Rarely if ever is the right side of the body involved. When cardiac causalgia major is present and the lungs are involved with "sterile" pneumonitis, the pneumonitis is always in the left lung and

rarely if ever in the right lung. The hoarseness associated with cardiac causalgia has not been studied adequately. I know if it is limited to the left vocal chord. I have that some patients develop a typical Horner's syndrome as a manifestation of cardiac causalgia. This syndrome has almost always involved the left eye and never the right eye. It is usually of short duration.

The distributions of these various manifestations of cardiac causalgia are as follows:

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Extracranial to intracranial microvascularization for the treatment of completed ischemic stroke

Extracranial surgery for internal carotid artery occlusion has had poor results, and attention has turned recently towards the possible improvement of cerebral blood flow by intracranial procedures. Jacobson and Suarez first used the operating microscope for anastomosing small vessel, and Donaghy reported seven human middle cerebral artery embolectomies using a T tube. Yasargil and Donaghy then performed the first successful extracranial to intracranial bypass in man. The end of the superficial temporal artery was anastomosed to the side of a cortical branch of the middle cerebral artery.

There has been a recent interest in the British press following leading articles in the *British Medical Journal* and in the *Lancet* and a report of results of this procedure for the treatment of completed ischemic stroke.

Extracranial to intracranial microvascularization has been performed mainly for transient ischemic attacks prolonged reversible neurological deficit progressing stroke and much less commonly for completed stroke. In Great Britain the procedure has not gained much popularity until recently. The feeling among many clinicians there has been that most patients considered for the procedure were far too well to merit angiography and bypass surgery. The procedure has recently become more popular and there has been less opposition to it for patients with completed ischemic stroke for whom nothing else could be offered.

In the recent report completed strokes occurred between 12 and 12 months (mean six months) before surgery. The

main deficits were weakness of the arm and physical intellectual deficit and to a lesser extent reduction in power in the leg. All patients were alert and had some evidence of retained function in the affected hemisphere. All patients had low density areas comparable with cerebral infarction on computerized axial tomography. The deficits were stable at the time of surgery and were thought unlikely to show further spontaneous improvement. A power record of the affected muscles, an assessment of the speech deficit and regional cerebral blood flow estimations were performed and were repeated after the operation. Psychological assessment was carried out before and after operation. The tests were of intelligence, verbal fluency (in the left sided cases) visual perception (in the right sided cases) and memory for both visual and verbal material.

The operation was performed by a vascular surgeon with experience in microvascular surgery with the assistance of a neurosurgeon. Using the operating microscope the end of the superficial temporal artery was anastomosed to the side of an appropriate cortical branch of the middle cerebral artery using interrupted 10/0 sutures.

All nine of the anastomoses remain patent as assessed by arteriography or directional Doppler probe with a patent anastomosis it is possible to feel the pulsation of the superficial temporal artery. All patients were alive and well at the time of writing and the procedure had an insignificant morbidity: there was no skin flap sloughing and the scar proved to be

Mitral prosthetic dehiscence and paraprosthetic regurgitation

To the Editor

In consequence of the case report by Chun and co workers concerning the Bjork Shiley mitral valvular dehiscence we would like to refer to our report of five patients with a Bjork Shiley mitral valve prosthesis and paraprosthetic regurgitation confirmed by cardiac catheterization, left ventricular cineangiography and reoperation. In four of these patients an abnormal anterior movement of the disc and the whole prosthesis, similar to that which Chun and associates described, was found at the beginning of diastole in the echocardiogram. Other echocardiographic findings were an increased left atrial diameter compared with preoperative or previous postoperative measurement, increased left ventricular end-diastolic and stroke volumes and normal systolic posterior motion of the interventricular septum with a wide amplitude. In two of these patients no murmurs were audible so that the paraprosthetic leakage may be insidious as previously described, and difficult to diagnose noninvasively without echocardiography. In cardiac catheterization, large v waves in the pulmonary capillary wedge tracings (30 to 60 mm Hg gradients across the mitral valve at the beginning of diastole and 20% to 50% mitral regurgitation fractions measured from quantitative left ventricular cineangiography were found in these patients. Also the time from the aortic valve closure sound to the opening sound of the mitral prosthesis (A_2 MVO interval) in the phonocardiogram was abnormally shortened (60 ± 10 msec) suggesting increased left atrial pressure.

Four patients were reoperated upon and in three of them the movement of the prosthesis in the echocardiogram was found to be normal after reoperation. Left atrial diameter, left ventricular end-diastolic and stroke volumes as well as the septal amplitude also decreased after successful reoperation. In one patient in whose echocardiogram the movement of the prosthesis remained abnormal after reoperation a slight residual paraprosthetic leakage was found in a later catheterization study.

Lately we have seen one more patient with paraprosthetic leakage confirmed by reoperation. Abnormal movement of the prosthesis in the echocardiogram was found and we have never seen an abnormal prosthetic movement like this with out paraprosthetic leakage. The appearance and magnitude of this abnormal anterior movement of the prosthesis in the echocardiogram seems to depend on the position and magnitude of the detachment of the prosthesis from the mitral annulus as well as on the pressure gradient across the mitral valve at the beginning of diastole. Because echocardiographic measurements in patients with normal prosthetic function did not change significantly after the first postoperative month we recommend the initial postoperative echocardiographic examination to take place up to the end of the first postoperative month in every patient with a mitral aortic prosthesis as a reference for later studies.

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Reply

To the Editor

We would like to thank Drs Ikaheimo and Takkunen for bringing to our attention their article containing a diographic illustration similar to ours of abnormal anterior movement of the Bjork Shiley disk at the beginning of diastole suggesting paraprosthetic mitral valve regurgitation. It seems Bernal Ramirez and Phillips at the same time published similar findings, referenced in our article. Because of the delay in SFDILINT Medline, MEDLARS and L. Medicus cataloging articles, our literature search was able to turn up the latter article prior to our submitting article and its acceptance for publication. The intent of our article was not to report another case of the echocardiographic features of Bjork Shiley valvular dehiscence but to encourage the use of noninvasive tools together in combination to detect paraprosthetic leaks prior to catheterization. The plain chest x ray and cinefluoroscopy as well as diography are invaluable in its recognition. In fact using our echo strips we found what one might even suspect be the intermittent appearance and disappearance of part of the prosthesis not previously illustrated (Figs. 1 and 2).

Furthermore we would like to suggest another noninvasive procedure also done in the case we reported although not exactly related to the patient's valvular dehiscence. In Swan Ganz catheter is already in position and the common acute pulmonary edema are entertained selective catheterizations of pulmonary arterial branches and hand injection of Renografin "60 may aid in excluding large pulmonary aneurysms as a cause (See Fig. 3).

In conclusion we strongly recommend pre and postoperative noninvasive studies and subsequent serial studies for the detection of prosthetic dysfunction. We may thus prevent or circumvent more serious complications from developing.

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causalgia are found within the same left dermatomes. The heart apparently is located within these dermatomes. These clinical manifestations conform with studies in experimental animals and man which show the role of the left stellate sympathetic ganglion and the other sympathetic ganglia of the left side of the neck and upper thoracic region in neural regulation of cardiac function. The mechanism for neurologic disturbances and location of the resultant manifestations needs careful study. It is interesting though that the distribution of the clinical manifestations of cardiac causalgia within the body is limited to certain left dermatomes. This distribution is thought provoking. It is tempting to conjecture the possible clinical beneficial effects for patients with cardiac causalgia that might be expected from procaine blocking or resection of left stellate sympathetic and upper thoracic sympathetic ganglia.

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type of cardiac arrhythmia for a brief period. She then remained well until the age of 21 years (1979) when she died suddenly unrelated to exertion. In neither case was there a family history of sudden death or heart disease but no clinical investigations were made of the other family members.

Although these two cases may simply identify me as an extremely rare" cardiologist who has encountered sudden death in multiple patients with mitral valve prolapse. I think the authors might well have downgraded their rating of sudden death prospects in this syndrome from "extremely rare" to "rare" or "uncommon." Perhaps the auscultatory findings of mitral valve prolapse carry a less favorable prognosis when heard in childhood than when initially heard in the adult years.

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Reply

To the Editor

We thank Dr Anderson for his interesting letter suggesting that mitral valve prolapse might carry a less favorable prognosis in childhood. We suppose that this is a possibility. The incidence of mitral valve prolapse increases greatly with age suggesting a "wear and tear" effect superimposed on a minor congenital abnormality of the cusp and chordal tissue. Maybe the valve abnormalities have to be more extreme to cause prolapse in children. On the other hand sudden death, presumably from dysrhythmias would be unlikely in the absence of myocardial disease or a prolonged QT interval. One of Dr Anderson's patients did indeed have an abnormal electrocardiogram but there is no note of the QT interval. Dr Anderson does not tell us about the necropsy findings.

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On rheumatic fever in children

To the Editor

I have read with interest the excellent review of Rheumatic fever in children by Dinachio and Taranta and congratulate the authors on their magnificent work. The subject and its geographic importance are well covered. The following comments, however are in order.

The disease continues to be a major cause of morbidity and mortality in the developing countries of the world. Among

the factors affecting the higher incidence of the disease in these areas the most important in my opinion are the unfavorable socioeconomic conditions. One would thus be inclined to look at the whole spectrum of these conditions. Obviously crowding in houses is a contributing factor so is the unavailability of proper medical care etc. But one often neglects the aspect of the spectrum is nutrition. Although there is evidence of a predisposing dietary deficiency in adult life the role of nutrition in the first six months of life in regard to rheumatic fever has not yet been thoroughly investigated. In my opinion there are some clues as to the possible role of nutrition in the first year of life in rendering a person susceptible to rheumatic fever. It has been shown that infantile malnutrition in the first six months of life leads to an imbalance of the immune system—i.e. B and T cell factors and complement production. Since autoimmune diseases are felt to result from such imbalances and rheumatic fever is favored by many as an autoimmune disease one can relate the two together and at least suggest that in the economically deprived populations where infantile malnutrition is quite common genetically susceptible individuals can become hypersensitized by immune imbalance and thus become an oversusceptible host. Future exposure to rheumatic streptococci in such individuals would result in an attack of rheumatic fever. The possibility that some serotypes of streptococci in areas of high incidence are more rheumatogenic is suggested by a 5% M typability in 100 strains of group beta hemolytic streptococci studies in an area of high incidence. The observation that the disease is rather rare in the Egyptian countryside as opposed to Cairo where the population live under conditions of extreme crowding is similar to our observations in Iran. We noted that over 60% of patients suffering from severe rheumatic heart disease were from urban and heavily populated areas and the majority had been born in these areas. Thus, the exposure of immigrants to unfamiliar serotypes is probably not always the case. But one would have to examine the factors created by crowding in such urban and overpopulated areas some of which probably play a role in the pathogenesis of the disease. Nevertheless it is known that infantile malnutrition is more common in urban communities than in rural areas where traditionally breastfeeding has continued to be practiced. Thus studies of the relation of nutrition in the first six months of life in making a host more susceptible to environmentally triggered autoimmune disease can open an avenue to the pathogenesis of rheumatic fever.

Our experience with over 1000 children with rheumatic heart disease showed that mitral stenosis was the second most common cause of isolated rheumatic valvular lesions accounting for more than 20% of the cases. In our series we have clearly distinguished between pure mitral stenosis and those stenoses associated with mitral regurgitation. All the children with severe mitral stenosis who underwent surgery were felt to have rheumatic valves (either during surgery or subsequent pathologic examination of the valves) and about 60% a history of rheumatic fever was elicited. In a few instances did the valve have the characteristics of congenital mitral stenosis. If one strongly argues a viral etiology for the disease as previously suggested it will have to be a beta hemolytic streptococcus-dependent virus otherwise such cases would have been observed elsewhere in the world.

As suggested by the authors, the Jones criteria with its boundaries between disease and non-disease states. As per

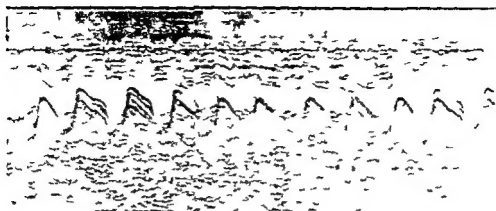


Fig 1 Echocardiographic tracing of prosthetic valve suggesting its displacement across the suture line

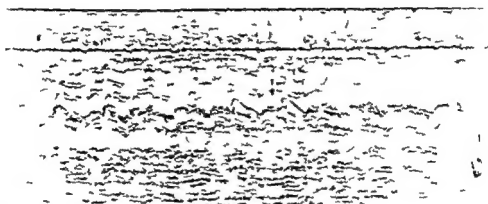


Fig 2 Another echocardiographic tracing illustrating a portion of the prosthesis appearing above the annulus



Fig 3 Chest x ray with selective injection of dye through a Swan-Ganz catheter into the right pulmonary arterial branches.

Idiopathic mitral valve prolapse and sudden death

To the Editor

In their review of mild mitral regurgitation and its most common cause mitral valve prolapse Leatham and Brigden conclude that sudden death is extremely rare. Unfortunately this has not been my experience inasmuch as I have encountered two sudden deaths among the approximately 50 children in whom I have made a diagnosis of idiopathic mitral valve prolapse. One was a girl whom I first examined at nine years of age eight months after her family physician had first heard a heart murmur on a routine examination. Aside from the late systolic murmur and click the only finding of note on interval examinations over the years was a flattening or inversion of the T waves in Leads 2 and 3. She had no symptoms until the age of 21 years (1974) when she developed palpitations, confirmed as ventricular premature beats by electrocardiography. Several days later and before any therapy had been started she died suddenly unrelated to exertion. The second case was a girl who had a typical late systolic murmur and click when I first examined her at seven years of age two years after her family physician had noted an abnormal heart sound. Her electrocardiogram remained normal over the years but at 19 years of age she had some

2. Bernal Ramirez J A and Phillips J H. Echocardiographic study of malfunction of the Bjork Shiley prosthetic heart valve in the mitral position. *Am J Cardiol* 40:449 1977.